IN THE UNITED STATES DISTRICT COURT

IN AND FOR THE DISTRICT OF DELAWARE

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IN RE BRIMONIDINE PATENT LITIGATION) **C.A. 07-md-1866-GMS**

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Wilmington, Delaware
Wednesday, March 11, 2009
9:00 a.m.
Day 3 of Trial

- - -

BEFORE: HONORABLE GREGORY M. SLEET, Chief Judge

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THE COURT: Good morning. Please be seated.

(Counsel respond, "Good morning.")

THE COURT: Now the witness can take the stand.

EDWARD KERSLAKE, having been previously sworn as a witness, was examined and testified further as follows ...

CROSS-EXAMINATION CONTINUED

THE COURT: Mr. Boggs, you have about ten more minutes. I am not going to hold you to that. But that's what you said yesterday. You go right ahead.

MR. BOGGS: Good morning, Your Honor. Thank you.

BY MR. BOGGS:

Q. **Good morning, Dr. Kerslake.**

A. **Good morning, Mr. Boggs.**

Q. **I would like to direct your attention to EBTX-166 in your binder.**

Do you recognize this document?

A. **Yes, I have seen this document a few times.**

Q. **In fact, we talked about this document during your deposition. Right?**

A. **We did.**

Q. **Do you recognize the author's name on this document?**

A. **I recognize the name David Small and Diane Tang-Liu as employees at the time. I don't recall Michelle Wong or Maria Dais.**

Q. **I am going to call this the "Small article." This article refers to a compound called AGN 191103. Correct?**

A. **I see that in the title, yes.**

Q. **Do you recognize that compound?**

A. **I don't recall.**

Q. **You --**

A. **I recognize the AGN number. But I don't recall what compound that is.**

Q. **Under the introduction portion on the first page, I would like you to look about halfway down the third paragraph. This paragraph refers to alpha-adrenergic agonists. Correct?**

A. **That's what it says.**

Q. **And that's exactly what brimonidine tartrate is. Right?**

A. **I can't recall directly.**

Q. **You don't remember that?**

A. **I am not sure if it was an alpha or an alpha-2. I am not sure of that. It's been eight, ten, 12 years.**

Q. **It's one of the two, though. Correct?**

A. **I believe so.**

Q. **Now, on Page 196, confirm for me that the Small article says that "AGN 191103 shows enviable potency in lowering intraocular pressure in rabbits and monkeys"?**

A. **That's what this document says.**

Q. **Now, David Small was a coworker of yours. Correct?**
A. **He worked in the preclinical group, I think, the pharmacokinetics group at Allergan. He was on the brimonidine X team, I think, if I recall.**
Q. **And you were on the brimonidine X team?**
A. **Yes.**
Q. **So he was a coworker of yours?**
A. **Yes.**
Q. **JTX-095, please. Dr. Kerslake, can you please look at JTX-095 in your binder?**
A. **I see that.**
Q. **Do you recognize this document?**
A. **I see my signature on it. It may have been one of the animal studies that Mr. Small did for us. I am not sure which one, the first or the second study that he did.**
Q. **So, David Small wrote this. Correct?**
A. **That's what it says, yeah.**
Q. **And you reviewed this document. Correct?**
A. **Yes.**
Q. **And that's your signature right on the front page. Right?**
A. **I see that, yes.**
Q. **Now, this report was written during the time that you were working to reformulate Alphagan. Correct?**
A. **It does mention brimonidine tartrate, which is the**

active that I was working with. So I would presume that, you know, given that my signature is on it and it pertains to that, then I would say probably yes.

Q. **Can you tell from the first page of JTX-095 whether or not it was the right time period?**

A. **Well, I see my signature of March, '98, which would correspond to a time when I was working on the brimonidine formulations. I can see that from my chart.**

Q. **You referred to the chart. A question came to my mind with regard to that chart. Do you have a date on there when you began working on the .15 formulation?**

A. **I do see a date there. May-June of 1998. It's that bottom bar there, listed as .15.**

Q. **And what document did you find that confirmed that date for you, do you remember?**

A. **I don't remember the specific documents. A lot of them are meeting minutes, lab notebook references. It was many hundreds of pages.**

Q. **But you don't remember, sitting here today, what document it is you used to confirm that that was the date you started working on the .15 formulation?**

A. **I don't know today. I think I have got references where we could probably find out which document it was.**

Q. **On direct examination, you didn't show us any documents that would confirm that. Right?**

A. **No.**

Q. **Now, with regard to the Small article -- to this report, excuse me, JTX-095, the title of this is "Comparison of Four Ophthalmic Brimonidine Tartrate Formulations to Alphagan in Albino Rabbits." Correct?**

A. **That's what it says.**

Q. **One of those formulations that was being compared was the brimonidine tartrate .2 percent in Refresh Purite. Right?**

A. **If you could show it to me in the document. I don't recall. Again, I haven't looked at this document in detail for many years.**

Q. **These are the formulations on Page 3 of 12 of the report that you were testing. Correct?**

A. **I see the formulations on Page 3.**

Q. **One of the formulations was brimonidine tartrate .2 percent Refresh Purite. Right?**

A. **I see that 7.4. Is that the second one? Yes, I see that.**

Q. **That had a pH of 7.4. Correct?**

A. **That's what it lists.**

Q. **Is that 9115X?**

A. **I can't be sure. Again, I haven't looked at this entire document. Does he specify that is what the formulation is in the document?**

Q. **This is what we know about it. Did you have another .2 percent formulation?**

A. **I can't recall this.**

Q. **Do you have another one listed on your time chart?**

A. **The .2 percent?**

Q. **Yes.**

A. **No, I only have one listed. But, again, it may not be an exhaustive list.**

Q. **When you prepared that chart, you went back and you found every formulation that you could find that you worked on. Right?**

A. **I went through and found every formulation that I could find but I am not sure it's an exhaustive list.**

Q. **And there is only one .2 percent formulation on that chart?**

A. **There is one .2 listed on that chart.**

Q. **This is the "Discussion" section of the report. Now, this is the report -- what is the purpose of these reports?**

A. **This is the result of an animal study that David would have conducted, Mr. Small would have conducted to help me with the different formulations we were looking at.**

Q. **Judging from the number of signatures on the front of the report, I would assume these are pretty important. Is that right?**

A. **They were expensive studies, so I am sure that they**

would want to make sure that that money was well-spent.

Q. In the third paragraph of the "Discussion" section, it reports that a "magnitude of increase in ocular concentrations produced by the Refresh Purite based-reformulation." Is that correct?

A. Would you say that again, please?

Q. In this portion --

A. I see that, yes. I see the line, the highlighted line.

Q. What does that mean?

A. What is the first?

If I could read the entire thing, I might have some context.

Q. Do you have it in front of you.

A. What page?

Q. The "Discussion" section of the report.

A. Okay.

(Pause.)

A. I need to be honest. I don't know what he is referring to here because he is talking about the first and the second formulation screen. If you want me to comment on this document, I would be much happier if I could read it.

Q. We talked about this document at length during your deposition, didn't we?

A. I don't remember the exact discussion at the

deposition. We talked about a broad range of things.

Q. **Confirm for me that your .2 percent formulation was described in this document as a simple solution?**

A. **I don't know that it was my .2 percent formulation. As I said, we did a number of different formulations and I can't guarantee that we only did one .2 percent formulation.**

Q. **There is only one on your chart. Right?**

A. **But I also said it wasn't an exhaustive list. It was the information I was able to find to try to be helpful in hundreds of pages, yes.**

Q. **And you only found one .2 percent?**

A. **I only listed one.**

Q. **You only listed one?**

A. **I tried to make it as simple as possible. I listed three comparable, I think there was five but I wasn't sure. I didn't want to put five, so I only put three to make it as simple as possible.**

Q. **So your timeline is not complete?**

A. **It is not an exhaustive list. I can't guarantee that.**

Q. **So we can't rely on this timeline. Is that right?**

A. **The information that is listed there, you can rely on. Information that is not listed there, I can't guarantee that it doesn't exist.**

Q. **Now, AGN 191103 is the methyl analog of brimonidine. Correct?**

A. **I have absolutely no idea.**

Q. **You don't remember anything about a methyl analog of brimonidine?**

A. **I do not. It's been 12 years. I can't remember.**

Q. **And in your work, going through the hundreds of pages of documents that you say you have done, you never found mention of this methyl analog. Is that right?**

A. **I specifically went through those documents to try and find times that we started working in formulations, or if they finished, why they finished, why we canceled them. I wasn't trying to review every document. It would have been physically impossible, with the time available, given how these time points were scattered through the documents.**

Q. **And in doing your timeline, you never found any attempts to formulate AGN 191103?**

A. **I don't recall doing so.**

Q. **David Small wrote a peer-reviewed journal article on 191103, and you didn't find any information at all about trying to formulate that compound?**

A. **Not in the documents I went through yesterday. I went through the meeting minutes of this brimonidine X team. I went through the notebooks that I had. I went through the available documents that I had to try to paint an accurate picture.**

Q. **This is Claim 1 of the '834 patent. Do you see**

where -- do you recognize this claim?

A. **The specifics of it, to be honest, if it's in my patent, then I would have been aware of it at one point. I can read it here.**

Q. **Dr. Kerslake, when I was taking your deposition, that wasn't the first time you had your deposition taken about these patents, was it?**

A. **No. I think I had it taken with the case against Alcon may be four or five years ago. Is that right?**

Q. **Yes, you did. And you just don't remember anything about this. Is that right?**

A. **You know, Mr. Boggs, when I was generating this chart, many of these formulations, which involved significant work, I couldn't remember until I saw the notebook reference in my technician book that reminded me of it. I am a smart guy. My memory is terrible. My wife will testify to that.**

Q. **You have a bad memory?**

A. **I do.**

Q. **I want to ask you a question about therapeutically effective. Animal studies in clinical trials would be necessary to determine what amounts of brimonidine tartrate would be effective to provide a therapeutic benefit to a patient. Correct?**

A. **Sir, I will say, as a layman, because it's been 12 years, and I am no expert, at least not anymore, but we had**

an Alphagan formulation that was out there that had a brimonidine tartrate in it at a concentration that was shown to be therapeutically effective.

In the animal studies that we did, we always compared it to Alphagan so we would know if you are delivering the drug to the eye at about the same proportion as Alphagan, then we would -- it's plausible that the formulation would be effective. It's not as if it was a brand-new compound that is coming to market for the first time and you have got no idea if it is going to work or not.

Q. On April 25th, 2005, you had your deposition taken in connection with the Alcon case. Right?

A. Yes.

Q. I think, if you look in your notebook, you will find the deposition transcript. Have you found it, sir?

A. I couldn't find it in the binder. But I can read it on the screen in front of me.

Q. Do you remember that deposition?

A. I do remember this, yes.

Q. That deposition was taken in Boston. Right?

A. I think so.

Q. It was taken at the offices of Fish & Richardson. Right?

A. Yes.

Q. And you were represented by counsel at that

deposition?

A. **There was somebody there from Fish & Richardson, if that's what you mean, yes.**

Q. **And you were under oath?**

A. **I was.**

Q. **Turn to Page 184 of that deposition transcript.**

A. **Can I just read it on the screen?**

Q. **You mentioned Mr. Tomasch?**

A. **That's right.**

Q. **He was the attorney representing Alcon. Is that right?**

A. **Yes, he was.**

Q. **I would like you to confirm for me that Mr. Tomasch asked you the following question and you gave the following answer.**

"Question: And it says in an amount effective to provide a therapeutic benefit to a patient.

"When you were at Allergan, did you do any work to attempt to determine what amounts of brimonidine tartrate would be effective to provide a therapeutic benefit to a patient?

"Answer: I don't remember.

"Question: Do you remember whether anyone on the brimonidine reformulation team did that?

"Answer: I can't be certain," is the answer.

"Question: Do you know how one would go about determining that?

"Answer: Animal studies, clinical trials."

Were you asked those questions and did you give those answers?

A. **I see the questions and the responses, yes.**

Q. **Did you -- were you asked those questions and did you give those answers?**

A. **If this is the transcript from my deposition, then, yes.**

MR. BOGGS: No further questions.

THE COURT: All right. Mr. Shear.

MR. SHEAR: Thank you, Your Honor.

REDIRECT EXAMINATION

BY MR. SHEAR:

Q. **Good morning, Dr. Kerslake.**

A. **Good morning.**

Q. **Do you still have in front of you JTX-44? It was given to you by Mr. Benson yesterday. It's not in one of the big notebooks. It was loose.**

A. **Yes. Yes.**

Q. **Yesterday, Mr. Benson referred you to the first bullet point under recommendations. Do you recall that?**

A. **Yes, I do.**

Q. **And he read to you the first sentence, "Develop a**

brimonidine/Purite formulation equal Refresh Tears plus .2 percent brimonidine"?

Do you recall that?

A. **Yes.**

Q. **Could you read aloud the second sentence of that bullet point?**

A. **"The issue will be the stability of the formulation due to potential for drug oxidation."**

Q. **What does that mean?**

A. **Purite, I don't recall the exact formula, but it's chlorinated -- it's an oxidative preservative, if I remember correctly. You know, my fear with an oxidative preservative was it was going to attack the active, the drug in this formulation, maybe make it inactive so it wouldn't work.**

MR. SHEAR: Thank you, Dr. Kerslake.

Your Honor, we have no further questions.

THE COURT: All right. Thank you, Dr. Kerslake. You are excused.

(Witness excused.)

MR. SHEAR: Your Honor, do you mind if Dr. Kerslake stays in the courtroom?

MR. BENSON: No objection, Your Honor.

MR. BOGGS: No objection.

MR. MARSDEN: Your Honor, may I clean off the witness stand.

THE COURT: Please do.

MS. BROOKS: Your Honor, Dr. Tanna, a witness for Apotex, has some scheduling issues. So we agreed that they can call him out of order even though we are still in our case-in-chief.

THE COURT: That is fine.

Mr. Breisblatt, who is going to examine?

MR. SODIKOFF: My name is Brian Sodikoff. I represent Apotex.

THE COURT: Mr. Sodikoff, what is the subject area?

MR. SODIKOFF: Dr. Tanna is a clinician who treats glaucoma patients.

THE COURT: Okay.

MR. SODIKOFF: Your Honor, may I approach the Bench?

THE COURT: Yes. Hold on just a second.

...ANGELO PETER TANNA, having been duly sworn as a witness, was examined and testified as follows...

MR. SODIKOFF: Your Honor, may I approach?

THE COURT: Yes. And you have leave to approach the witness freely, counsel.

MR. SODIKOFF: Thank you, Your Honor.

DIRECT EXAMINATION

BY MR. SODIKOFF:

Q. Good morning. Dr. Tanna, can you please tell me your current position?

A. I am director of the glaucoma service at Northwestern University Medical School.

Q. How long have you held that position?

A. Since July 1999.

Q. Dr. Tanna, if you could open up your notebook, the first tab, marked as DTX-306A, can you tell me what this is?

A. This is my CV.

Q. And if I represent to you that this is the CV taken from your expert report, would you verify that this information is accurate?

A. Yes.

Q. I would like to just quickly go through some of your qualifications related to glaucoma and glaucoma treatment.

Dr. Tanna, where did you attend medical school?

A. Columbia University College of Physicians and Surgeons.

Q. And from what years did you attend that school?

A. From 1990 to May 1994.

Q. What did you do after graduating medical school?

A. I took my internship in internal medicine at the Graduate Hospital in Philadelphia.

Q. Is that hospital associated with any university?

A. **At the time, it was associated with the hospital of the University of Pennsylvania.**

Q. **And what did you do after completing your internship?**

A. **I took my residency in ophthalmology at the Wilmer Eye Institute at Johns Hopkins Hospital.**

Q. **What year did you begin your residency?**

A. **In 1995.**

Q. **When did you complete it?**

A. **1998.**

Q. **What types of things does a resident at Johns Hopkins do in the opthalmopathy program?**

A. **One immerses one's self in the medical aspects of ophthalmology, including the diagnostic and management of ophthalmic disease processes.**

Q. **Did you treat patients who suffered from glaucoma?**

A. **I did. The patient population that we served had a very high prevalence of glaucoma.**

Q. **What did you do after completing your residency at Johns Hopkins?**

A. **I did a fellowship in glaucoma, also at Johns Hopkins.**

Q. **What does one do during a fellowship?**

A. **During fellowship, although one continues to manage general ophthalmological problems and general medical problems, one is focused in the management and diagnosis of the glaucoma disease processes.**

Q. **So your residency is ophthalmology generally and your fellowship more focused on glaucoma specifically?**

A. **Correct.**

Q. **What did you do after completing your fellowship?**

A. **I was recruited to become director of the glaucoma service at Northwestern University Medical School.**

Q. **What kind of training do you get during your fellowship at Johns Hopkins?**

A. **During fellowship, one sees, in my case, almost exclusively patients with glaucoma, some of whom have diagnostic challenges pertaining to glaucoma. Some of whom have therapeutic challenges pertaining to the disease.**

So one is involved in seeing many, many patients with glaucoma, diagnosing and managing the disease process.

Q. **Did you administer or prescribe eyedrops to patients?**

A. **I did.**

Q. **Are you familiar with the eyedrop medications that were used to treat glaucoma in this time frame before 1999?**

A. **Yes.**

Q. **Approximately how many patients were you treating during your fellowship?**

A. **During my fellowship, hundreds of patients. I also had my own glaucoma practice at one of the Johns Hopkins' satellite facilities called Johns Hopkins Bayview Medical Center. And I oversaw the care, a day-and-a-half a week, of**

glaucoma patients there. So I would say actually during that year, I probably took care of over a thousand patients with glaucoma, well over a thousand.

Q. **Dr. Tanna, are you board certified?**

A. **I am.**

Q. **Which board?**

A. **The American Board of Ophthalmology.**

Q. **Are you licensed to practice medicine?**

A. **Yes, I am, in the State of Illinois.**

Q. **Dr. Tanna, after completing your fellowship, I believe you said you moved on to Northwestern.**

Can you tell me what you did there?

A. **I assumed a position as the director of the glaucoma service.**

Q. **What are some of the responsibilities of the director of glaucoma service?**

A. **I oversaw the clinical management of patients with glaucoma and patients suspected of having glaucoma. I also oversaw the clinical research in glaucoma at Northwestern.**

Q. **Have you been at that position since July of 1999?**

A. **Yes, I have.**

Q. **Do you have any other faculty appointments?**

A. **Well, my faculty appointment is at Northwestern. I am assistant professor of ophthalmology.**

Q. **What do you do as an assistant professor of**

ophthalmology?

A. **I teach ophthalmology in general for medical students. I also train residents and fellows regarding matters in glaucoma.**

Q. **Dr. Tanna, I am on Page 2 of your CV. It mentions "Editorial Board Membership."**

Can you tell me briefly what that is?

A. **I am on the editorial board of three journals: Survey of ophthalmology, techniques in ophthalmology, and also ophthalmology management.**

Ophthalmology management is what we would classify as a throw-away type magazine. It's one that is used to educate general ophthalmologists in the community regarding the practice of various aspects of ophthalmology.

Q. **Dr. Tanna, have you published any articles?**

A. **I have.**

Q. **Have you published any articles that are specific to brimonidine tartrate, the drug at issue here?**

A. **I have one article that pertains are directly to that. The lead author is Robert Feldman. I was the second author on that paper. It was published in ophthalmology in 2007. It was the result of a multi-center clinical trial that was designed to compare the efficacy and safety of brimonidine-Purite 0.15 percent versus brinzolamide, another class of glaucoma medication, when used as add-on therapy**

with a prostaglandin analog.

Q. **Dr. Tanna, have you been involved in the writing of any book chapters?**

A. **I have.**

Q. **Can you tell us briefly about that?**

A. **I have written several book chapters. I have two that I am working on right now. Almost all of them pertain to glaucoma.**

Q. **In addition to your work as chief of the glaucoma service, do you have any staff appointments at other hospitals?**

A. **Yes. I am an employee of the VA Medical Center in Chicago. And I am also on staff at Children's Memorial Hospital in Chicago.**

Q. **What do you do at the VA Medical Center in Chicago?**

A. **I supervise the residents' care, the residents in our training program manage the patients directly, and I supervise that care as it pertains to glaucoma.**

Q. **What do you do at Children's Memorial Hospital in Chicago?**

A. **I manage patients with glaucoma, children with glaucoma, who have failed the primary surgical modalities that are used by the pediatric ophthalmologists who really run the show there. So if there is a patient with whom they are having a specific problem that they can't handle, I**

manage those patients.
Q. So you kind of serve as an expert to them for more complicated cases?
A. Correct.
Q. Do you consider yourself, as of 1999, an expert in glaucoma and the treatment of glaucoma?
A. Yes, I do.
MR. SODIKOFF: Your Honor, Apotex would tender Dr. Tanna as an expert to give opinions in this case.
MS. BROOKS: Your Honor, we have no objection to Dr. Tanna tendering opinions as an expert in the field of glaucoma. We would have objections to Dr. Tanna tendering any opinions as an expert, of one of skill in the art of the particular patents involved.
THE COURT: Is that going to be an issue?
MR. SODIKOFF: I don't think so, Your Honor.
THE COURT: That is fine. The doctor is accepted as offered.
BY MR. SODIKOFF:
Q. Dr. Tanna, earlier in this trial, we have gone over some of the treatment options and stuff regarding glaucoma. I would like to go over just a little of it briefly to kind of ground your testimony.
Can you tell me just briefly what is glaucoma?
A. Glaucoma is an optic nerve disease in which elevated

intraocular pressure is thought to be a major causative risk factor.

What happens in the glaucoma disease process is there is damage to the optic nerve, which we can see on direct examination, that results in a characteristic change in the appearance of the optic nerve called cupping. That occurs in association with a characteristic pattern of vision loss.

Q. **If we can call up, Mr. Rosenberg, ADX-3.**

Can you tell me what causes glaucoma?

A. **Well, it's a multi-factorial disease. What we know now is that elevated intraocular pressure is a major causative risk factor.**

Q. **What is elevated intraocular pressure?**

A. **If you think about the pressure in the eye as being analogous to the pressure in a tire, for example, the pressure in the eye, if it is too high for that particular eye, and this varies depending on the individual patient, because some patients with elevated intraocular pressure do not develop glaucoma and others with what we would think of as being normal intraocular pressure do go on and develop glaucoma. At any rate, elevated intraocular pressure results in damage to the optic nerve.**

Q. **Is that kind of reflected in the bottom middle drawing there?**

A. **It is schematically represented in that drawing on the left.**

Q. **How does one treat glaucoma?**

A. **The only proven means of successfully treating glaucoma is by lowering the intraocular pressure.**

Q. **How do you, as a physician, lower intraocular pressure?**

A. **There are three different broad categories of approach. The most commonly used is the use of medications, particularly eyedrops, to lower the intraocular pressure. We can also use laser surgery techniques and incisional surgical techniques.**

Q. **I would like to focus on eyedrops, because I think that's kind of the focus of this litigation.**

Back in 1999, were there glaucoma eyedrops that were available for treating glaucoma?

A. **Yes. There were seven different classes of medications available in 1999 and prior to that.**

Q. **Were you aware of each of those medications?**

A. **Yes, I was.**

Q. **Is it your opinion that those of skill in the art would be aware of those different options?**

A. **Yes.**

Q. **I would like to turn to the next tab in your book, DTX-295, two tabs further.**

Dr. Tanna, can you tell me what this article is?

A. **Yes. This is an article that was published in 1998 in the New England Journal of Medicine. The lead author is Wallace L.M. Alward. He is at the University of Iowa. He is a very well-respected glaucoma expert. It describes the medical management of glaucoma. It is a review article that is really aimed toward non-ophthalmologists.**

Q. **Dr. Tanna, turning to the numbered Page 1301. I think it's the fourth page of this document. Can you tell me what this page describes?**

A. **This page summarizes the beta adrenergic antagonists drugs, also known as beta-blockers.**

Q. **Were these beta-blockers known to you as one of skill in the art before 1999?**

A. **Yes.**

Q. **Can you look at Table 2 of this document?**

A. **Yes.**

Q. **What does Table 2 tell you?**

A. **This summarizes or lists the medications in this particular class.**

Q. **Are you -- were you aware of these medications back before 1999?**

A. **Yes, I was.**

Q. **Which medications did you prescribe most frequently out of this list?**

A. **Timolol has always been the most frequently prescribed, at least in the United States, out of this list. Though, in Japan, carteolol may be more commonly prescribed.**

Q. **What does this table tell you about the availability of timolol back before 1999?**

A. **In terms of the concentrations available, it tells us that timolol was available in two different concentrations, 0.25 percent and 0.5 percent.**

Q. **Turning to the next page of this document, I think you mentioned prostaglandin analogs. Can you tell us briefly what those are?**

A. **Those are currently the most commonly prescribed medications. They were available prior to 1999 as well. They lower the intraocular pressure by increasing the amount of fluid that can leave the eye through one of the pathways called the uveoscleral pathway.**

Q. **Can you tell me what the next subheading here is?**

A. **Adrenergic Agonist Drugs.**

Q. **Looking at Table 3, are you familiar with those drugs?**

A. **Yes, I am. Many of them are available in different concentrations.**

Q. **Brimonidine -- is the brimonidine there the brimonidine tartrate?**

A. **Yes. It's referring to the original formulation in Alphagan.**

Q. **That was available before 1999. Correct?**

A. **That's correct.**

Q. **I would like to turn two pages further.**

THE COURT: Doctor, that table that we were just looking at, where I see brimonidine, is that brimonidine tartrate, or is there a difference? Are we talking about the same thing?

THE WITNESS: Yes, Your Honor. We are talking about the same thing. It is referring to the original formulation, which we have just been calling Alphagan.

BY MR. SODIKOFF:

Q. **Just while we are still there in Table 3, what is apraclonidine?**

A. **Apraclonidine was commercially known as Iopidine. It still available. It is an another alpha-2 selective adrenergic agonist. So it is in the same class and even the same subclass as the brimonidine. It was available in two different concentrations, 0.5 percent and 1 percent.**

Q. **Turning to the next page, 1303 on the bottom, this page mentions carbonic anhydrase inhibitors.**

Can you tell me what those are?

A. **That is a class of compounds that lowered the intraocular pressure by reducing the amount of fluid produced inside the eye. And these are available most commonly as eyedrops but they are also available in oral or**

intravenous forms.

Q. **Turning to the next page, it mentions cholinergic agonists. Can you tell me what those are?**

A. **The cholinergic agonists are a family of compounds that bind to a receptor on the muscles in the ciliary body, the muscarinic receptor. That causes contraction of those muscle fibers. And some of those muscle fibers attach to a part of the drainage pathway that causes the drainage pathway to physically open up. And this results in a reduction in pressure by way of an increased amount of fluid flow out of the eye through the trabecular meshwork.**

Q. **Looking at Table 5, are you familiar with the different medications listed there?**

A. **Yes, I am.**

Q. **Were those medications available in the formulations that are listed?**

A. **Yes, they were.**

Q. **Looking at pilocarpine hydrochloride, the second one listed as a direct-acting cholinergic agonist, were those concentrations all available to you before 1999?**

A. **They were, but I only used the 0.25, 0.5, 1, 2, 4, and 6 percent concentrations. The other ones, although they were available, were fairly rarely and uncommonly used.**

Q. **Was it uncommon for a certain medication to be available in multiple formulation strengths?**

A. **No. Several of them were available in multiple concentrations.**

Q. **Overall, how many different, if you can approximate, how many different medications for glaucoma were available before 1999?**

A. **I remember calculating this for Mr. Shear during my deposition. I can estimate. But I cannot tell you exactly. When you asked me that, would you mean to count generics and brand name products as two separate?**

Q. **First, how many different classes of medications?**

A. **There are seven classes of medications.**

Q. **And do some of those classes have subcategories?**

A. **Yes, definitely. For example, we would call the cholinergic agonists, which are described in this table, we can subclassify them as direct acting and indirectly acting.**

So there are subclasses for some of them. Not for all.

For example, the prostaglandin analogs, I consider just one class, prostaglandin analogs.

Q. **Dr. Tanna, I believe you were here when Dr. Whitcup was testifying about how brimonidine tartrate works. Were you here for that part?**

A. **I did not hear him discuss that particular part.**

Q. **Well, he mentioned a dual mechanism of action for brimonidine tartrate. And he looked at ADX-14. If I can**

put that back on the board.

Can you give me a basic description of what we see in this demonstrative?

A. **Well, despite the title, what this demonstrates is what we would call aqueous humor dynamics. This is at a basic level that medical students, I would expect a medical student to understand.**

Can I touch the screen?

This part of the eye is called the ciliary body. These are the areas in which the fluid that is produced by the eye is secreted into the eye.

So fluid flows into the eye here, and then, typically, it travels in between the iris, which varies in color, depending on the individual, from blue to brown, and the lens, the lens is the part of the eye that, as it becomes cloudy, we call cataract.

So the fluid flows in between, and then it flows through the pupil and then into the front chamber of the eye called the anterior chamber. In the anterior chamber, there are two exit pathways, effectively. One is the classic pathway. That is called the trabecular meshwork. The other is the alternate pathway, or the uveoscleral pathway. And fluid has to travel through the ciliary body face and can exit the eye through that pathway. The dual mechanism of action of brimonidine refers to the fact that brimonidine

reduces the production of aqueous humor at the ciliary body and also increases the facility with which the fluid can exit the eye through the trabecular meshwork -- through the uveoscleral pathway.

Q. **Dr. Tanna, you have mentioned a lot of structures here. I can't personally remember them. I just wonder, is it your opinion that this is all well-known to those of skill in the art before 1999?**

A. **Yes, it was well-known prior to 1999. There was a publication by Carol Torres from Carl Camras lab at the University of Nebraska in Omaha which described this dual mechanism of action in 1995.**

Q. **So the fact that brimonidine stops the production of aqueous humor and then also allows it to leach out easier, that was known before 1999?**

A. **Yes, it was.**

Q. **If I could guide you to DTX-11, which is the next tab in our book?**

A. **Yes.**

Q. **Is this the article that you just referred to?**

A. **This is the article I referred to.**

Q. **When was this article published?**

A. **1995.**

Q. **What is the conclusion of the article?**

A. **The conclusion states that brimonidine -- excuse me.**

I am going to read it verbatim. The brimonidine induced reduction in IOP, which refers to intraocular pressure, in humans is associated with a decrease in aqueous flow and an increase in uveoscleral outflow.

Q. **I would like to guide you to JTX-100, which is the next one in our chart here. Can you tell me what this document is?**

A. **This is a document that lists the components of various formulations of Alphagan, including what is here referred to as the original Alphagan, which is the 0.2 formulation that has been discussed in the courtroom. That's all the way on the right. And, also, Alphagan P 0.15 percent, which was the marketed Alphagan P. That's the second column.**

Q. **Okay.**

A. **I am sorry. It is the one to the left of the one that was just highlighted.**

Q. **So the one to the right, that is the original Alphagan formulation. Right?**

A. **Correct.**

Q. **That was available before 1999?**

A. **Yes, it was.**

Q. **So if I refer to that as the prior art Alphagan formulation, will you understand that's what I am talking about?**

A. **I will.**

Q. **Now, the prior art Alphagan formulation, or just eyedrops generally, eyedrops with active ingredients, what are they generally made of?**

A. **Well, an eyedrop is typically composed of an active ingredient or maybe more than one active ingredient, there are some combination products, along with a vehicle. And the biggest component of most eyedrop vehicles is water. But the other components I consider a vehicle, too.**

That includes a preservative, a viscosity building agent, buffers that will stabilize the pH of the solution, and also electrolytes, which affect the tonicity of the overall solution.

Q. **Looking at JTX-100, can you circle what you would consider the vehicle?**

A. **For the original Alphagan formulation?**

Q. **For the original Alphagan formulation, thank you.**

MS. BROOKS: Your Honor, I am going to object to this. I believe this is outside Dr. Tanna's area of expertise and now we are getting into formulations.

MR. SODIKOFF: I am just briefly touching that, in Dr. Tanna's practice, people refer to that as the vehicle and the top part as the active ingredient.

THE COURT: Fair enough. I will overrule that objection. You can answer that question, Doctor.

THE WITNESS: Can you repeat the question?

THE COURT: Repeat the question as you just framed it.

BY MR. SODIKOFF:

Q. **As one of skill of the in the art before 1999 --**

THE COURT: I think he is a practitioner.

BY MR. SODIKOFF:

Q. **As a practitioner, before 1999, would you refer to what you have circled there as the vehicle for original Alphagan?**

A. **Yes, from BAK down to purified water.**

Q. **And what would you refer to as the, if anything, as the active ingredient?**

A. **The active ingredient is brimonidine tartrate.**

Q. **Dr. Tanna, have you formed any opinions in this case regarding the original Alphagan?**

A. **Yes, I have. I have formulated three broad opinions regarding original Alphagan.**

Q. **Can you please tell me what your first broad opinion is?**

A. **The first opinion is that one of skill in the art prior to July 1999 would have been motivated --**

MS. BROOKS: Objection, Your Honor.

THE COURT: I think we are now in that area where Ms. Brooks originally indicated there would be a

dispute, if the witness were called upon to discuss, to present himself as one skilled in the art. I thought we had agreement that wasn't going to be an issue.

MR. SODIKOFF: He is not one of skill in the art. But I think that his opinion and testimony is going to show that one of skill in the art was aware of what clinicians looked for in vehicles.

THE COURT: That is why he is a clinician. Right?

MR. SODIKOFF: Yes. But also that one of skill in the art --

THE COURT: Let's go over here and talk about it.

(The following took place at sidebar.)

MR. SODIKOFF: Your Honor, we are not going into much. What we would like to do is show as a clinician he would look at this molecule and the Alphagan formulation. He is going to comment on what he likes and doesn't like about the vehicle.

As a clinician, we think that also has some impact on one of skill in the art because they are formulators who are trying to sell these drugs to clinicians.

THE COURT: That may be an argument that you can make. I think Ms. Brooks essentially is saying, look, we

didn't understand that he was going to discuss, have a discussion as one skilled in the art. It may be semantics, it may not be.

MR. SODIKOFF: I think it is. Maybe I can clear it up.

THE COURT: Ms. Brooks.

MS. BROOKS: Yes, Your Honor. We believe that what Dr. Tanna is going to try to do is say what one of skill -- I think he just started to say what would have been obvious to one of skill in the art and what one of skill in the art would have been motivated to do.

THE COURT: And you have an objection to that?

MS. BROOKS: Yes, Your Honor.

THE COURT: And at the outset of the testimony it didn't appear there was going to be a dispute about that.

I think, if you rephrase the question, if you perhaps approach it from a different angle, rather than asking him as one skilled in the art, unless we need to have a debate about that.

MR. SODIKOFF: I think we do, Your Honor.

I don't think any of the experts by either side are technically one of skill in the art. What they are here to do is shed their expertise on what they believe one of skill in the art would be motivated to do. What I would like to show with Dr. Tanna --

THE COURT: Are we talking about one of skill in the art of formulations and reformulation?

MR. SODIKOFF: Yes. But for us, one of skill in the art also understands not just formulating but they also look to how that is actually used to treat patients. You are formulating for a reason.

THE COURT: You would hope that medical doctors would understand that.

MS. BROOKS: So, Your Honor, first of all, I beg to differ. Our experts actually are all one of skill in the art. And they have prepared their experts where they define who one of skill in the art is and they fall within that definition.

Dr. Tanna in his expert report said that he relied on their expert, Dr. Banker's definition of one of skill in the art. And Dr. Banker has a very lengthy definition of that. Dr. Tanna doesn't meet it. I would cite the Court to just one example -- there is plenty of them -- but the Sundance v. DelMonte case at 550 F.3d 1356, where the Federal Circuit held that it was an abuse of discretion to permit a witness to testify as an expert on the issues of noninfringement or invalidity unless that witness is qualified as an expert in the pertinent art. Testimony proffered by a witness lacking relevant technical expertise fails the standard of admissibility under Federal

Rule of Evidence 702.

Indeed, where an issue calls for consideration of evidence from the perspective of one of ordinary skill in the art, it is contradictory to Rule 702 to allow a witness to testify on the issue who is not qualified as an expert, technical expert in the art.

It goes on on the next page and specifically addresses obviousness: Nor may a witness not qualified in the pertinent art testify as an expert on obviousness or any of the underlying technical questions, such as the nature of the claimed invention, the scope and content of the prior art, the differences between the claimed invention and the prior art, or the motivation of one of ordinary skill in the art to combine these references to achieve the claimed invention.

THE COURT: I am going to let Mr. Breisblatt weigh in here a little bit.

MR. BREISBLATT: Your Honor, that is a pre-KSR case, I suspect.

MS. BROOKS: Actually, December of 2008.

MR. BREISBLATT: But the underlying thing is, this expert is fully qualified. He has gone over his qualifications for the very area we are here for. The area we are here for is treating the eye. The formulation part of it, because these claims are geared to formulation, are

not done in a vacuum, as Mr. Sodikoff has said.

THE COURT: He has framed your position.

I will let you get back in.

All of this, there has been plenty of time in the lead-up to being here to either have raised this with me or to have discussed it among yourselves. So I would expect there has been some discussion. You have exchanged expert reports. Clearly, the rules provide ample opportunity for, as Ms. Brooks points out, for experts to be identified in their fields.

If he has not been identified as one skilled in the art, and if this is a surprise to the other side, I am not going to permit it. It sounds like that's what is happening.

MR. SODIKOFF: It is not a surprise at all, Your Honor. If I can grab his report and quote it.

THE COURT: Sure.

MR. BREISBLATT: I was going -- it has nothing to do with this issue. I just want to note to the Court that this is Mr. Sodikoff and Mr. Benson's first trial. I appreciate the Court's patience.

THE COURT: I fully recognize that. It is fine. You got to start somewhere. A Bench trial is the best place to start.

MR. SODIKOFF: The opinions formed, A, what was

known in the field of ophthalmology regarding the use of ophthalmic medications specifically in regard to the use of a formulation containing brimonidine for reducing intraocular pressure.

B. Whether a person of ordinary skill in the art would have an apparent reason or motivation to provide an ophthalmic solution containing a compound known to effectively lower intraocular pressure with a preservative known to be well tolerated and less toxic to the ocular surface than the prior art formulations or had a reasonable expectation of success that they could do so without undue experimentation.

THE COURT: This is the doctor's report.

MR. SODIKOFF: Yes, sir. They deposed him on this report. Further, throughout the report, and what we plan on having him testify, is that there was a disadvantages to BAK, and that was known in the art. And he believes that that would motivate someone to switch and not use BAK because it was known to be toxic.

THE COURT: You are familiar with that.

MS. BROOKS: I am, Your Honor. Here is our response. We have no objection to Dr. Tanna talking about what was known in the field of ophthalmology. The balance of his report, where he talks about in his personal experience how BAK has an allergic effect, how he prefers

Purite, why that would motivate him as an ophthalmologist to use a BAK-free medication, we have no objection to any of that. It's when he starts talking about what one of skill in the art would or would not have done.

THE COURT: You have got an expert to counter their expert on this area.

MR. SODIKOFF: Yes. For most of it. My point is, Dr. Tanna -- and I can ask him about this -- advises medical companies.

THE COURT: That is fine. But I am not going to let him testify beyond his expert report. There are reasonable inferences that a fact-finder can draw from his testimony. I understand what your argument is. It's just that the rules shouldn't permit -- I am not going to allow a breach of the rules. If the report -- let me ask you this, Ms. Brooks: Given the sentence --

MR. SODIKOFF: The report is very clear. He went into excruciating detail on this.

THE COURT: What counsel just read, in Section 2, Opinions Formed, that sentence that you are familiar with, that he just read into the record -- let me take another look at it.

(Pause.)

THE COURT: It does use the terms of art, one of ordinary skill in the art who is asked to opine and

formulate an opinion on whether one of such skill would have a reason or motivation to provide an ophthalmic solution containing a compound known to effectively lower intraocular pressure and a preservative known to be well tolerated and less toxic to the ocular surface than prior art formulations or had a reasonable expectation of success --

MR. SODIKOFF: He goes through excruciating detail --

THE COURT: -- without undue experimentation.

This would seem to be the kind of question, if he answered it, that should permit him to testify as one of skill in the art in addition to being an expert clinician, don't you think?

MS. BROOKS: He certainly set that out as one of the questions. But then when we get into the bulk of his report, it is all done from the perspective of the ophthalmologist. And he has no idea whether -- when he talks about expectation of success, he is not talking about expectation of success in the formulation. He is talking about expectation of success in the patient.

THE COURT: The treatment.

MS. BROOKS: In the treatment. We have no objection to any of that.

What we do have an objection to is him getting into whether the formulators would have been motivated based

on what they knew about Purite, based upon what they knew about brimonidine, based upon what they knew about carboxymethylcellulose --

MR. SODIKOFF: Their claims, we have looked at them all day and week, say a therapeutically effective amount. Who determines therapeutically effective? That is a clinician. That is a doctor. That is not a formulator. One of skill in the art, that is a relevant inquiry as to what is a therapeutically effective amount, what would a clinician look for to find a medication that is therapeutically effective and the best one possible.

THE COURT: What is your reaction to that?

MS. BROOKS: My reaction to that is that is one aspect of the claimed invention, the claimed invention that has multiple elements dealing with polyanionic polymers, dealing with brimonidine tartrate, dealing with quinolines --

THE COURT: Mr. Breisblatt, you got to calm down. I am having a talk with this young man. You are chomping at the bit.

MR. BREISBLATT: I am excited, Your Honor.

THE COURT: Understanding what you just said, clinicians, nevertheless, don't they rely on formulators? They don't formulate in realtime. They are given concentrations of medicines, or a range, maybe, that are

made available to them. And they make determinations, I guess they have to have some knowledge about chemistry, they are physicians, but they are not expert in the area of formulations. Aren't they relying on formulators to give them therapeutically effective drugs?

MR. SODIKOFF: I would say no. Dr. Tanna advises pharmaceutical companies. They call him and say, what is a better preservative from the clinical data?

That is the kind of thing that a clinician does. They are involved.

THE COURT: I am sure the formulators constantly are in touch with practitioners. That makes sense.

MR. SODIKOFF: They are getting feedback. They take doctor's notes.

THE COURT: But for purposes of evidence today and issues of fairness and surprise and all of those -- and I am not making a ruling that they have been surprised --

MR. SODIKOFF: I feel like I have been surprised with this objection, to be honest.

THE COURT: You shouldn't be surprised by any objection made in court.

Mr. Breisblatt.

MR. BREISBLATT: Your Honor, I finally got a chance to look at the case. We need to understand that the expert witness we are talking about here was Mr. Bliss, a

patent law expert. And we know how the Court feels about patent law experts.

THE COURT: I know how I feel about patent law experts.

MR. BREISBLATT: This discussion and their rules dealt with the fact that Mr. Bliss, this patent lawyer, began giving opinions. We are not talking about a technical guy.

THE COURT: Is that true?

MS. BROOKS: This particular case, Your Honor. We wanted to find a post-KSR citation for Your Honor. This is 2008. We can give Your Honor a plethora of cases that hold the same proposition.

THE COURT: That makes sense. Mr. Breisblatt's point is the language here deals with not the ilk of expert --

MS. BROOKS: That's correct, Your Honor. They are talking about a patent law expert.

THE COURT: It may be the case that the doctrinal language, the precepts, the standards that are outlined and articulated by the Court apply equally. That makes sense to me.

MS. BROOKS: That would be our position.

THE COURT: But I think I am going to try to split this baby a little bit, because we don't have time for

me to read through the expert report. One of Ms. Brooks's contentions, counsel, is that while the proposition is set out in Paragraph B in the manner just read into the record, that the report -- I know you two differ on this. She says it addresses the issue from the standpoint of a clinician and not a reformulator, and given that they were not, I assume you are going to say, motivated, and did not examine him during deposition in that regard --

MS. BROOKS: We actually did examine him to the extent he has absolutely no formulation experience. He has never formulated. He has never done pre-formulation. We did examine him to that extent and then simply elicited the basis of his opinion, which is all from the ophthalmologist's perspective.

THE COURT: Okay. I am going to let him testify. It's a Bench trial. In a jury trial, I might not.

I think I am able, will be able to, especially given this discussion, should it come to pass that I am more persuaded to your point of view, I will be able to filter out that testimony.

So I am going to let him testify. We have got him here. I think that's the better solution.

MS. BROOKS: Thank you, Your Honor.

MR. SODIKOFF: Thank you, Your Honor.

(End of sidebar conference.)

BY MR. SODIKOFF:

Q. **Let's get re adjusted here. We are looking at the active formulation. You commented that you see an active ingredient and a group vehicle below?**

My question to you is: Do you have an opinion regarding the use of BAK in this formulation?

A. **Yes, I do. Benzoalkonium chloride was known prior to July 1999 to have toxic effects on the surface of the eye. So my opinion is that one of skill, if I may use that language, Your Honor, would have been motivated prior to July 1999 to attempt to use an alternative preservative, one that is safer and gentler on the surface of the human eye.**

Q. **Dr. Tanna, just to go back again to your expertise, have you presented at glaucoma symposiums and other conferences regarding glaucoma?**

A. **I have. I presented at various scientific meetings, including ARVO, which is the Association of Research and Vision Ophthalmology. That's actually my primary place of presentation. But I have also done various presentations on behalf of drug companies, including presentations that specifically deal with the toxic effects of benzylalkonium chloride.**

Q. **When your at these conferences, are they generally attended by people from the drug companies, themselves?**

A. **They are present at these meetings, yes.**

Q. **Do you present information regarding, for example, the toxicity of BAK at a meeting such as this?**

A. **I have -- at the types of meetings I just described, scientific meetings, for example, what we call ARVO, the annual meeting of the Association of Research and Vision Ophthalmology, I have -- the closest I have come to presenting something relating to formulation is a paper on the thermal stability of three different prostaglandin analogs.**

Regarding benzoalkonium chloride, I haven't published anything or presented anything at scientific meetings that specifically deals with benzoalkonium chloride. However, I did serve as a consultant to Alcon regarding the reformulation of travoprost, which was one of the prostaglandin analogs that was originally formulated with benzene alconium chloride, and is now available both traditionally formulated with benzoalkonium chloride and also reformulated with a newer, gentler preservative.

Q. **Can you just generally tell me, I don't want to get into Alcon's confidential information, but what your role was as a consultant with Alcon?**

A. **To guide them regarding the potential value of such product. And also, I used that preservative, alternatively preserved product, which is now called Travatan Z, on a compassionate use basis on two patients prior to its FDA**

approval. So I did deal with parts of the NDA for that product. I submitted my own IND to the ADA regarding the use of that product in two patients.

And because of my early experience with it, I was asked to present at various meetings, that were commercial meetings that Alcon conducted throughout the United States, to promote that new product when it did become approved.

Q. I believe you mentioned that -- let me go back to ask what your opinion of BAK is.

A. Benzoalkonium chloride, BAK, is known to have toxic and proinflammatory effects on the surface of the human eye.

Q. What is your opinion regarding BAK based on?

A. It is based on peer-reviewed literature published before July 1999.

Q. Can I guide you to the next tab, DTX-283?

A. Yes.

Q. Can you tell me what this is?

A. This is a paper that was published by the group Moorfields Eye Institute in London in the British Journal of Ophthalmology in 1993. It is called, "Adverse Effects of Topical Anti Glaucomas Medications on the Conjunctiva."

Q. Where was this journal published?

A. British Journal of Ophthalmology.

Q. When was it published?

A. **1993.**

Q. **Is this a well-read journal?**

A. **Yes, it is an important journal, even in the United States.**

Q. **What do the authors describe in this report?**

A. **This was a study that was designed to determine if the chronic use of antiglaucoma medications in patients who are about to have filtering surgery or glaucoma surgery has an adverse impact on the success rates of that surgery.**

Q. **Do the authors make any conclusions regarding BAK specifically?**

A. **The authors attribute -- may I say the finding of the paper first?**

Q. **Sure.**

A. **The authors reported that the use of chronic antiglaucoma therapy was a risk factor for failure of glaucoma surgery. And they were able to determine that because there were a group of patients who underwent surgery first without previously undergoing medical glaucoma therapy. That is in fashion, particularly at Moorfields and in Europe.**

So what the authors report, again, was that the success of surgery was better in the group of patients who had not previously undergone glaucoma therapy.

Then, to answer your original question, if I

may, the authors attribute at least some of that increased failure in the group of patients who underwent therapy to benzoalkonium chloride.

Q. **If I can turn to page 594 of this article, the column on the right-hand side.**

Can you briefly summarize what this column states?

A. **This is part of the discussion. And, briefly, they support further previously published invitro evidence, or laboratory data, that shows the potential mechanism by which this human observation could be explained. One is, one paper refers to the toxicity of benzoalkonium chloride on the cells at the surface of the human eye. And the other reports on the fact that invitro, fibroblasts, which are scar tissue forming cells, proliferate with exposure to benzoalkonium chloride. That is bad for glaucoma surgery because scar tissue is what you don't want when you have glaucoma surgery, at least not excessive scar tissue.**

Q. **Dr. Tanna, have you had the opportunity to review any other articles regarding BAK?**

A. **I have. I have reviewed some of the work by Christophe Baudouin at the University of Paris.**

Q. **If I can guide you to DTX-337, the next tab in this book.**

A. **Yes.**

Q. **Can you tell me the title of this article?**

A. **"Effects of Benzoalkonium Chloride on Growth and Survival of Chang Conjunctival Cells."**

Q. **Looking at the bottom of this document, can you tell me when and where it was published?**

A. **It was published in Investigative Ophthalmology and Visual Science in March 1999. And that is a prominent journal.**

Q. **Can you tell me what the purpose of this study was?**

A. **This was an invitro study in cells in tissue culture designed to determine the toxicity of benzoalkonium chloride on those cells.**

THE COURT: Counsel, do you have an extra copy of 337? It doesn't seem to have made it into my book.

MR. SODIKOFF: I apologize, Your Honor. I am sure I do.

THE COURT: That's all right.

MR. SODIKOFF: I think we just looked at the purpose of the study.

BY MR. SODIKOFF:

Q. **Dr. Tanna, what was the conclusions of the study?**

A. **The results and the conclusions demonstrated that even at very low concentrations of benzoalkonium chloride, as low as 0.0001 percent, there was toxicity, cytotoxicity, cell death, of these conjunctival cells. And conjunctival cells**

is a membrane on the surface of the eye. Conjunctivitis refers to inflammation of that membrane, the membrane that covers the white part of the eye.

Q. **What was the concentration where these problems were seen?**

A. **Even as low as 0.0001 percent. At very, very low concentrations, benzoalkonium chloride is toxic to these cells.**

Q. **Can you see there what the concentration of BAK is in the original Alphagan formulation?**

A. **It is listed as 0.005 percent weight volume.**

Q. **Turning to DTX-281, the next article that you have, can you tell me what this is?**

A. **This is a paper that was published also in March 1999 in the Journal of Ophthalmology, that is an American journal. It is a very big paper that has two major groups of experiments that address the issues of benzoalkonium chloride.**

Q. **Benzoalkonium chloride, just for the rest of us, is BAK. Correct?**

A. **That's correct.**

Q. **And what did the first study find regarding -- I guess what was the test done for the first study?**

A. **Well, I am going to break it down into two, and I will call the first one the human study. What was done in that**

study is patients who were about to undergo glaucoma filtering surgery were enrolled into the study, and they had biopsies performed of their conjunctiva at the time of surgery.

What took place was the patients who were enrolled were on either multiple eyedrops for more than one year, on just one eyedrop for more than one year, or on no previous eyedrops.

What was found is that there was more inflammation in the conjunctival biopsies in the group of patients who had previously been treated with glaucoma therapy.

So there was some evidence at that point to attribute that to benzoalkonium chloride but the patients were also getting the medicinal aspect of the active ingredients of the eyedrops.

Q. **What was done to determine if it was the BAK or the medicinal component that was causing the problem?**

A. **The separate animal study was done in rats, in which rats were exposed to either just benzoalkonium chloride, a control vehicle excluding the benzoalkonium chloride, or an eyedrop component. I believe it was a beta-blocker, either timolol or carteolol, with benzoalkonium chloride.**

Q. **What was the finding of that second animal study?**

A. **That there was more inflammation in the eyes that**

received either the medication plus benzoalkonium chloride and there was a similar amount in the eyes that received just the benzoalkonium chloride.

This isolated the benzoalkonium chloride as at least a component of the proinflammatory effects that was observed in the clinical study.

Q. **Dr. Tanna, knowing this about BAK -- and all these articles were published before July 1999. Correct?**

A. **Correct.**

Q. **The last three?**

A. **Yes.**

Q. **What would you think about a way to improve a medication that included BAK as a preservative?**

A. **One would be motivated to try and switch to a gentler preservative that is less toxic and less inflammatory to the human ocular surface.**

Q. **Now, I believe you said that BAK causes, just generally, let's call them disadvantage in toxicity issues. Is that fair to say?**

A. **Toxicity and inflammatory.**

Q. **Is that a problem in relation to glaucoma patients specifically?**

A. **Yes, in that glaucoma medical therapy is generally considered lifelong or very long duration medical therapy, so there is a lot of chronic exposure to benzoalkonium**

chloride.

If somebody has an infection on the surface of the eye, they maybe on an antibiotic for a week or maybe two weeks. If that antibiotic contains benzoalkonium chloride, it is not a big deal for the long-term health of the eye, but given the chronic nature of the glaucoma therapy, I think it is a substantially larger issue.

Q. **Dr. Tanna, have you heard of the term "dry eye"?**

A. **Yes, I have.**

Q. **What is dry eye?**

A. **Dry eye is a very common medical condition in which patients have symptoms such as burning, a foreign body sensation, sometimes blurry vision that is attributable to a deficiency of, or an abnormality of the natural tear firm of the eye ocular surface.**

Q. **How do you treat a patient with dry eye?**

A. **The most common first line of treatment is with replacement artificial tears.**

Q. **Before 1999, what was your preferred artificial tear for the treatment of dry eye?**

A. **Prior to 1999, Refresh Tears was my preferred artificial tear supplement.**

Q. **And were you alone in that preference?**

A. **I think Refresh was extremely popular.**

Q. **Do glaucoma patients sometimes have dry eye?**

A. **Yes, they do. Dry eye is a disease that is more common as people get older, and glaucoma is, too. And both of them are relatively common diseases. They are not rare diseases. And, so, both diseases coexist in a substantial proportion of patients with glaucoma.**

Q. **I would like to look at DTX-290, the next tab.**

Could you tell me what this is, Dr. Tanna?

A. **This is a relatively recent paper. It was published, I think, in 2007. It was published in the Journal of Glaucoma -- it was published in 2008, from Robert Weinreb's group at UCSD. It shows that there is a very high prevalence of what's called here "ocular surface disease," which includes dry eye in, in glaucoma patients.**

Q. **When was this article published, just so we are clear?**

A. **2008.**

Q. **So this is not prior art to the patents at issue. Is that correct?**

A. **That's correct.**

Q. **Is this article consistent with what you saw in your practice before 1999?**

A. **Well, this showed a very high prevalence of 59 percent. And I would not have really guessed that it was quite that high. I would have thought more like 30 to 40 percent.**

But it is consistent. We knew that lots of

patients with glaucoma had dry eye. We knew that those two disease processes coexisted in a large proportion of patients.

Q. **You referred to "we" there. Who are you referencing?**

A. **I am referring to glaucoma physicians, even ophthalmologists in general, without being glaucoma experts in particular.**

I think that it was widely known among clinicians that these two diseases coexisted. It was common knowledge.

Q. **Before 1999, did you personally treat patients who had both glaucoma and dry eye?**

A. **Yes, definitely.**

Q. **How often did that occur?**

A. **I don't know how to quantify it. A lot of my patients who had glaucoma also had dry eye.**

Q. **Did you ever prescribe a patient who had both glaucoma and dry eye Alphagan, the original formulation?**

A. **Yes.**

Q. **Before 1999, before Alphagan P came out, did you prescribe Alphagan?**

A. **I did, I used it extensively.**

Q. **And did you prescribe to -- I would like to talk about the specific subset of patients that had both dry eye and glaucoma.**

How would you treat that patient?

A. **So, some of those patients would be on Alphagan, but not all, by any means. And some of those, I would say everybody with dry eye would be receiving Refresh Tears.**

Some of them would get Refresh Tears, which was the product preserved with Purite. And some of them would be on Refresh Tears of the preservative-free variety or maybe some other brand of artificial tears that was preservative-free.

Refresh was the only brand that was preserved, the only brand of artificial tears that was preserved that I recall recommending to patients prior to July, 1999, but there were several that were preservative-free that I used.

Q. **Before 1999, you were prescribing Alphagan, the original formulation, and Refresh Tears to the same patient. Is that correct?**

A. **To many patients, I recommended use of both of those medications. Correct.**

Q. **Can you describe what you saw as the result of that treatment?**

A. **I didn't see any problems attributable to Refresh Tears, attributable to using both of those in the same patient.**

Q. **Did any of your patients somehow suffer from glass shard-like cutting of their eye when you treated -- when you**

prescribed both Refresh Tears and Alphagan?

A. **No, I don't remember that. The only patient who told me that an eyedrop felt like glass in the eye was a different medication. It was one patient who did report that. I remember very clearly, it was a different medication.**

Q. **If we can go back to JTX-100, just on the board for a second.**

Dr. Tanna, are you -- looking at this vehicle again for the original Alphagan prior art formulation, can you tell me what it states as the tonicity agent?

A. **The tonicity agent is listed as sodium chloride.**

Q. **What is a tonicity agent?**

A. **Tonicity, osmolality, and osmolarity are all related. They basically give you an idea of the concentration of salt in the solution. And tonicity is important because it regulates the flow of water into and out of cells.**

Q. **Sodium chloride, is that basically table salt?**

A. **Sodium chloride is table salt.**

Q. **Now, in the Alphagan formulation, only sodium chloride is listed as a tonicity agent and there are no electrolytes. Is that correct?**

A. **Correct. Some would say that sodium chloride is itself an electrolyte.**

Q. **There is no other electrolytes besides sodium**

chloride?

A. **That's correct.**

Q. **Was there literature out -- let me take that back.**

As a practicing clinician before 1999, were there certain other electrolytes that you would have liked to have seen in a vehicle?

A. **Yes.**

Q. **I would like to turn to DTX-279. Could you tell me what this article is, Dr. Tanna?**

A. **This is a 1985 paper called Essential Ions for Maintenance of the Corneal Epithelial Surface by Bachman and Wilson.**

Q. **The corneal epithelial surface, that is basically the eye?**

A. **The surface of the eye. The corneal surface, the cornea is the front clear part of the eye. There are other components to the ocular surface as well.**

Q. **If we can look at the abstract here with the sentence that starts, "It was shown," can you tell me what that states, about five lines down?**

A. **It says, "It was shown that the epithelial surface was maintained best with a buffered solution containing potassium, calcium, magnesium, phosphate, and bicarbonate, in addition to sodium chloride."**

Q. **The potassium, calcium, magnesium, are those what we**

have been calling electrolytes or tonicity agents?

A. **Yes.**

Q. **What year was this article published?**

A. **1985.**

Q. **That is seen on, I believe, Page 3 at the top.**

Going back to Page 2 of this article and looking at the first column, at the top, the first paragraph, do you see where it says, "A basic tear solution"?

A. **Yes, I do.**

Q. **What did the authors here include in their basic tear solution? It might be easier to look at Table 1 for this part.**

Do you understand "BTS" is a basic tear solution as these authors call it?

A. **I do understand that, yes.**

Q. **What does this solution contain?**

A. **The basic tear solution contains sodium chloride, potasium chloride, calcium chloride, that .2 H-20 means dihydrate, magnesium chloride, hexahydrate, sodium carbonate, and sodium phosphate.**

Q. **Going back to the full page, on the left-hand side, the second paragraph, can you tell me what the os -- what is osmolarity?**

A. **Along with tonicity and osmolarity, they are all related terms with simple differences in terms of the**

precise detail of how you calculate it that basically give you the concentration of salts in the solution.

That is a simplification of it as it applies to eyedrops that we are talking about.

Q. **Here it reports that the osmolarity was 305. Is there a significance to that specific number?**

A. **Yes. It is very close to the osmolarity of the normal human tears.**

Q. **Was that known before 1999?**

A. **Yes, it was.**

Q. **Why would you want to have the osmolarity, or tonicity, close to that of the human tears?**

A. **Because if you were far away from that of the normal human tear film, it would be painful. It would burn or sting. That's because it would either drive water out of the cells, of the surface of the eye, or force water in, depending on which direction it was off.**

Q. **The next line here says that the pH of the buffered solutions was adjusted to 7.5.**

First of all, does this suggest that the solutions that they were talking about were buffered?

A. **Yes.**

Q. **And what is the significance of a pH of 7.5?**

A. **7.5 is close to the pH of the human tears.**

Q. **Going to the next page, at the top again, what year**

was this paper published?

A. **1985.**

Q. **So this was all known, in addition to before 1999, it was also known as of 1985. Is that accurate?**

A. **That's accurate.**

Q. **I would like to move to the discussion section of this. Why don't you tell me first, what did the authors, what did they do here? What was the basis of this report?**

A. **They, they looked at the corneal surface with these different solutions and then looked at light scatter to get an idea of the impact of these different solutions on the surface of the eye.**

Q. **Let's go to the "Discussion" section on Page 1487, the bottom right.**

A. **To be complete, I should say, this was in rabbits. It was done in rabbits.**

Q. **Are rabbits, to your knowledge, a normal model for use for looking at eye medications?**

A. **It's commonly used, an excellent model for that purpose.**

Q. **Looking at the bottom right-hand side, potassium has a high concentration in tears. Does that suggest that was known in 1985?**

A. **Yes, it does.**

Q. **What do the authors conclude about the use of potasium**

in an artificial tear solution?

A. **They conclude that potasium should be included in an artificial tear solution because it was the most important factor, it seemed, in this particular study with respect to maintaining stability of the ocular surface.**

Q. **And looking at the top of Page 1488, the next page of this document, the very top, the first sentence of the paper, does that accurately reflect the authors' conclusion regarding the use of potassium in an artificial tear solution?**

A. **Well, that fragment, I am not sure, can accurately reflect anything.**

Q. **Can you show me 1487 and 1488, split screen.**

On the bottom of 1487, you can see that the "it" is referring to potassium. Is that accurate?

A. **That's what the authorize is talking about here, yes.**

Q. **So the authors conclude and teach us that potassium should be included in tear substitutes.**

Is that an accurate conclusion?

A. **That is their advice based on the results on their, their findings and based on previous publications.**

Q. **Looking at the, if we can go now and focus on Page 1488, the next paragraph, if you can highlight that, do the authors reach any conclusions about the presence of calcium and magnesium electrolytes in artificial tear solutions?**

A. **It is their opinion, and they state it right here, that there is a strong suggestion that calcium, magnesium, bicarbonate, and phosphate should also be included.**

Q. **Do you disagree with their conclusions?**

A. **Not at all.**

Q. **Do you agree with them?**

A. **I do.**

Q. **So, Dr. Tanna, I believe you said earlier that you treat patients who have dry eye. I guess I just have a hypothetical question for you. If you were to -- if you had two artificial tear solutions in front of you, one included only an ACL, sodium chloride, and the other one included sodium chloride, potassium chloride, calcium, and magnesium, which would you prefer?**

A. **One would prefer the more complex electrolyte composition that you have described.**

Q. **Why is that?**

A. **Because of the beneficial effects of those electrolytes on the ocular surface. It's been previously demonstrated. And because it more closely mimics the natural tear film.**

Q. **Was all that known before 1999?**

A. **Yes, it was.**

Q. **I would like to turn to DTX- -- actually, we are going to skip DTX-336.**

Let's move on to DTX-297. Dr. Tanna, did you have an opportunity to review this document in preparing for your testimony today?

A. **I did.**

Q. **And what is this document?**

A. **This was an invitro study that looked at the effect of different viscosity building agents on the stability of cells in culture. So it was a cytotoxicity study of a corneal cell line.**

Q. **When was this paper published?**

A. **This was published in 1998, I believe.**

Yes, 1998.

Q. **So far, except for the one paper that talked about the prevalence of dry eye patients also having glaucoma, have all the articles we have been discussing been published before 1999?**

A. **All of them before July 1999. We had a couple published in March 1999.**

Q. **Thank you for being precise.**

What does this paper tell us about -- what was the purpose of this paper?

A. **It was to compare these two viscosity building agents, the carbomers versus the cellulose-based viscosity building agents, of which carboxymethylcellulose is one, in terms of toxicity on cells in culture.**

Q. **What is the conclusion of this paper?**

A. **The conclusion is that the carbomer-based molecules are cytotoxic and that the carboxymethylcellulose ones were much less toxic.**

Q. **Dr. Tanna, just to be clear, when you read these articles, do you feel like you are qualified to understand and interpret what they are teaching us?**

A. **Yes, I do.**

Q. **Thank you.**

I would like to turn to Page 439 of this document. These don't have Bates numbers, but 439, and the beginning of the last full paragraph on the left-hand side that starts with "Several studies," did you consider this paragraph in forming your opinions for this case?

A. **I did.**

Q. **What does this paragraph teach us?**

A. **It states that several studies have shown the advantages of anionic polymers, such as CMC, which is carboxymethylcellulose, that are more bioadhesive than neutral polymers.**

Q. **What does "bioadhesive" mean?**

A. **Well, it refers to this concept that -- and it is particular important for artificial tears, that the longer the retention time on the surface of the eye, the more effective the therapy, because, with dry eye, you are**

chronically trying to keep the surface of the eye as moist as possible. So, if you have simply water in a salt solution, it's going to wet the surface of the eye and then the eye is immediately going to dry off.

So, especially as it pertains to artificial tear therapy, you want material that is going to hang onto the surface of the eye. The surface of the eye is very complex. And, so, there are opportunities to use molecules like carboxymethylcellulose that will hang on effectively longer.

Q. **This hanging on or bio adhesion of carboxymethylcellulose, would it also be relevant to patients who are suffering from both glaucoma and dry eye?**

A. **It would be relevant for glaucoma in that, by prolonging the duration of time that a medication solution can, if you will, hang onto the surface of the eye, you increase the likelihood that a molecule will be able to cross into the eye.**

Q. **If we can go back to JTX-100. If we can just look at the Alphagan original formulation. This is the prior art Alphagan formulation, Dr. Tanna. And after looking at everything we have looked at, what is your opinion regarding the use of BAK and whether there are any motivations that you see in relation to that use?**

A. **Well, given the publications that we looked at, and there are still others we didn't look at, prior to July,**

1999, there is evidence in the literature of the toxicity and proinflammatory effects of benzoalkonium chloride. So I believe one would be motivated to try and reformulate as many eyedrops as possible with gentler, milder preservatives, like Purite.

Q. **And you were actually using Purite in the form of Refresh Tears to treat a significant subset of your patient population. Is that correct?**

A. **That is correct. I was not really, per se, using Purite. I was using the entire artificial tear formulation, which it happened to be preserved with, you are right.**

Q. **Dr. Tanna, it's Apotex position that one of skill in the art would be motivated to combine the original Alphagan with the vehicle of Refresh Tears.**

Is there anything that would dissuade one of skill in the art from trying that combination?

A. **No.**

Q. **If I could guide you to DTX-011. Can you tell me what this is, from the front page?**

A. **It is called, Development Pharmaceutics Report for Brimonidine-Purite Ophthalmic Solution, Issued June 22, 2000, Volume 1 of 4.**

Q. **If we could turn --**

MR. SODIKOFF: Your Honor, this is an abbreviated form of this exhibit. It is not the whole

thing. I believe it's like the first 15 or 16 pages. It extends through AGN 0059806. We definitely cut off a lot of it, because it was very thick.

BY MR. SODIKOFF:

Q. If I can guide you to AGN 59801. The second sentence under the composition and the formulation development, can you read to me what Allergan told the FDA its reason for using Refresh Tears was?

A. The highlighted portion says, "As a consequence, formulation studies targeted incorporating brimonidine tartrate at 0.1 percent, 0.15 percent, and 0.2 percent weight to volume, using Refresh Tears vehicle as a platform."

I am not sure I answered your question.

Q. I guess when Allergan was talking to the FDA to try to get approval of its drug, it said that Refresh Tears was the vehicle for brimonidine. Isn't that what this says? This was eventually sent to the, I believe there is similar language in their NDA.

I will take that question back, Your Honor.

Q. The next sentence there, "Refresh Tears is an over-the-counter lubricant eyedrop with sodium carboxymethylcellulose as an ophthalmic demulcent and the non-irritating preservative Purite."

Is that consistent with your opinion of Refresh

Tears before 1999?

A. **Yes, it is.**

Q. **And going to the next paragraph, at least by the date of this article, which is June 22nd, 2000, before the filing dates of the four latter patents, can you tell me what concentration of brimonidine tartrate Allergan had chosen to pursue FDA approval of?**

A. **This states, "The finished product contains brimonidine tartrate at 0.15 percent weight to volume."**

Q. **Dr. Tanna, I think you have been here for a lot of the week. The .15 percent concentration, and I think it was actually reflected in the exhibit we had up yesterday that was hard to see, was chosen well before the summer of 2000.**

Does that sound accurate?

A. **Yes, it does.**

Q. **Do you have an opinion as to whether the Allergan inventors properly disclosed the best mode of their invention for their patents?**

A. **I do --**

MS. BROOKS: Your Honor, I am going to object at this point.

THE COURT: Sustained.

BY MR. SODIKOFF:

Q. **If we can go back to JTX-100. Dr. Tanna, in the original formulation of Alphagan, the concentration of the**

brimonidine tartrate, the active ingredient, was.2 percent. Is that correct?

A. **That is correct.**

Q. **Do you have an opinion as to whether one would be motivated to try to lower that concentration?**

A. **Yes, I do. With the data available in the literature prior to July, 1999, there was substantial evidence that brimonidine was similarly effective at lower concentrations, at least at some time points when the measurements were done in clinical trials.**

We also know, from previously published studies, that the incidence of adverse events and the severity of adverse events was dose-related.

So, given those two facts, I believe that one would have been motivated to try to reduce the concentration of brimonidine, the active ingredient, in a new formulation of Alphagan, or brimonidine, that would result, one would expect, in a reduction in adverse events and possibly no reduction in efficacy.

Q. **If we could turn, Dr. Tanna, to DTX-63. Can you tell me what this is, Dr. Tanna?**

A. **This is the front cover -- not the front cover, but the inner page, inner front page of a multi-volume textbook called The Glaucomas. I believe it was published in '96, but I am uncertain about that.**

Q. **I think this version is actually missing the copyright date.**

MR. SODIKOFF: Your Honor, would you mind if we supplemented the record after this trial with the copyright date of this?

THE COURT: Is there any objection, Ms. Brooks?

MS. BROOKS: No objection, Your Honor.

MR. SODIKOFF: Just to keep the record clear.

BY MR. SODIKOFF:

Q. **If we can turn to Page 1441 of this document, AGN 5388 -- let's go to 5387 first.**

A. **That page number is what.**

Q. **It's 11440 of the journal.**

A. **It's a textbook, by the way.**

Q. **I apologize. Are textbooks usually on the Vanguard of what's known in the art? Do they usually lag behind journals?**

A. **Big-time lag with textbooks.**

Q. **So if this was published in '96, would you have an opinion as to whether this was known well before that time?**

A. **Yes. I think that the information that's in this chapter would have been known well before '96, if '96 is the correct date. But again, I don't recall for sure the publication date.**

Q. **We will assume it is before 1999 for today.**

In the top right, it mentions brimonidine. Is that the brimonidine tartrate that we have been talking about?

A. **Yes.**

Q. **It's relatively selective alpha-2-agonists?**

A. **Yes.**

Q. **It has a structure similar to Clonidine?**

A. **Correct.**

Q. **It is also known to be a lipophilic drug?**

A. **Yes.**

Q. **If we can look at the next page of this document, I would like to look at the adverse events description for brimonidine. The first paragraph. Can you tell me what this paragraph reports about the adverse events for brimonidine tartrate?**

A. **Shall I read it?**

Q. **You can summarize it for us.**

A. **It basically says that these common side effects that occur with brimonidine, dry mouth, conjunctival blanching, which is just a constriction, and, therefore, whitening of the conjunctiva, and drowsiness, that they appear to be dose-related. Meaning, the higher the concentration, the higher the likelihood of the particular side effect being mentioned.**

Q. **Is the flip-side of that true for dose-related, that**

if you lower the concentration, you would expect to have less side effects?

A. **Yes, that's what that means.**

Q. **I would like to look at DTX-111, please. Can you tell me what this article is?**

A. **Yes. This is a paper published, the lead author is Robert Derick, it is published in the Journal of Ophthalmology in 1997. It is called, "Brimonidine Tartrate, a One-Month Dose Response Study."**

By the way, since it was published in 1997, and since, I believe, the previous chapter refers to it, I doubt that the previous chapter was published as early as '96, now that I am reminded of this. And I just don't remember what year the book was published.

Q. **But this article was definitely published before 1999?**

A. **Definitely, yes.**

Q. **Looking at the bottom left of the article, if you can blow that section up, the second-to-last line, can you tell us who supported this article?**

A. **Supported in part by a grant from the Anvyl Krieger Foundation and Allergan, Inc.**

Q. **That is the plaintiff here?**

A. **Correct.**

Q. **Can you tell me what the authors found on this article relating to safety?**

A. **The authors found that there was a fairly high incidence of side effects related to the use of brimonidine. Maybe I should say that, in this study, there were three different concentrations of brimonidine that were tested.**

Q. **So this study was testing to see whether there would be a different amount of side effects for different concentrations of brimonidine?**

A. **Not just side effects. They were also looking at the effectiveness in terms of pressure reduction.**

Q. **But it includes the side effects. What were the three concentrations of brimonidine that were chosen?**

A. **In increasing order, 0.08 percent, 0.2 percent, and 0.5 percent.**

Q. **And the Alphagan marketed product, which one of those three is it?**

A. **The middle one, 0.2 percent.**

Q. **So this also tested a concentration less than what was marketed as Alphagan. Is that accurate?**

A. **It did, 0.08 percent was a lower concentration, right.**

Q. **That is actually a lower concentration than Alphagan P that is on the market. Is that accurate?**

A. **That is accurate. Alphagan P is available at 0.1 percent or 0.15 percent.**

Q. **And this is 0.08 percent?**

A. **Correct.**

Q. **If I can turn you to Page 134 of this article, the paragraph on the left, can you tell me what this describes?**

A. **It says, Conjunctival blanching appeared to be dose-related. It was observed bilaterally in eight patients in both the 0.2 and 0.5 percent treatment groups.**

Q. **How much in the .08 group?**

A. **Five patients in the .08 group.**

Q. **So it was less than in the .08 than in the .2 or the .5?**

A. **Correct.**

Q. **What is conjunctival blanching? Is that an adverse effect?**

A. **Some would consider it a favorable effect in some ways, because what happens initially, with brimonidine, is there is a constriction of blood vessels. But in reality, that initial constriction leads to a later dilation of blood vessels. There is this rebound dilation. So the blanching is the whitening aspect that occurs immediately after dosing. And then, later, there is, the eye is red, there is conjunctival hypererythema.**

Q. **If we can look at the next sentence, conjunctival --**

A. **Conjunctival erythema. That is redness.**

Q. **This is causing red eye. Can you tell us what the authors report in this Allergan-supported study about the adverse events of red eye in different concentrations?**

A. **It says it occurred more commonly with higher concentrations of brimonidine than with the lower concentration, occurring in eight of 48 patients in the 0.5 percent group, six of 48 patients in the 0.2 percent group, and only two of 45 patients in the 0.08 percent group.**

Q. **So there is one-third, or 66 percent less patients in the .08 group who suffer this adverse event compared to the .2 percent?**

A. **That's correct.**

Q. **If we can go back to the big part of this page and look at the last paragraph before the discussion. This paragraph mentions burning and stinging. That seems to be a be problem.**

Can you describe what this reports about that?

A. **It also reports this dose response effect in which the side effect is more common at the 0.5 percent dose than at the 0.2 or 0.08 percent dose.**

Q. **Looking at the last sentence of this paragraph, it discusses dry mouth and fatigue-drowsiness. What is dry mouth?**

A. **The technical term is xerostomia, and it is a side effect that is associated with the use of the alpha-2-adrenergic agonists, including brimonidine.**

Q. **What, if anything, does dry mouth give you a picture of relating to the global or systemic adverse events**

relating to brimonidine?

A. **I actually think of dry mouth as being somewhat of a local adverse event because the normal pathway for tears to flow away from the eye, including medications that you would add to the tear film, is through a drainage pathway in the eyelids, into the nose, and then into the mouth.**

So when this medication comes into contact with alpha-2 receptors in the mouth, that leads to oral dryness.

Q. **So, can you tell us what this article reports about the incidence of dry mouth?**

A. **It is also, it follows a dose response pattern in which it's less common at the lower concentrations and much more common at the highest concentration, the 0.5 percent concentration.**

Q. **So it's 13.3 percent in the .08 and 16.7 in the .2. Is that accurate?**

A. **Correct. And 35.4 in the .5 concentration.**

Q. **And how about fatigue-drowsiness?**

A. **That I think of as being a systemic adverse event because the drug actually has to get into the bloodstream in order to cause fatigue and drowsiness. It actually has to cross the blood brain barrier and affect the central nervous system directly.**

Q. **Were you here when Dr. Whitcup was talking about the problem of fatigue and how brimonidine shouldn't impact how**

you are able to drive your car or operate machinery?

A. **I did not hear that part of his testimony. I think I heard just the tail maybe hour of his testimony, if I remember correctly.**

Q. **Is this a serious side effect, fatigue-drowsiness?**

A. **It can be. There is a warning on the bottle not to use heavy machinery and that sort of thing.**

Q. **What was the incidence of fatigue-drowsiness as you go up the dose curve from .08 to .2 to .5?**

A. **There is a clear dose response effect in which it increases with increase in concentration from 6.7 to 10.4 to 29.2 percent.**

Q. **So looking just at the safety of brimonidine tartrate, just the safety aspect, which is better, the .2, the -- the .08, the .2 or the .5?**

A. **Well, because the lower the concentration of brimonidine, the lower the incidence of side effects, regarding just side effects, the 0.08 percent group did the best.**

Q. **And as a doctor, are you always trying to lower the incidence of side effects?**

A. **Yes. That's one goal in therapy.**

Q. **Now, I think you mentioned that this article also looked at the efficacy of these different concentrations. Is that correct?**

A. **Yes, that's correct.**

Q. **Again, this article was published in 1996 or '97, well before the filing dates of the four latter patents. Is that correct?**

A. **That is correct.**

Q. **I would like to guide you to Page 132, the "Results" section, and the last sentence there, can you tell me what that says?**

A. **"All concentrations of brimonidine significantly reduced IOP," intraocular pressure, that is, "from baseline at all followup visits."**

Q. **Does this basically mean -- when it says "all concentrations," what is that referring to?**

A. **It is referring to 0.08 percent, the 0.2 percent, and the 0.5 percent concentrations of brimonidine.**

Q. **And this is on the bottom of Page 132?**

A. **That's correct, bottom right.**

Q. **If I could do a split screen with this page here, and then JTX-003, the first claim. Claim 1. If you could blow up the last sentence that we looked at.**

So in 1997, Allergan reports, or in this Allergan-sponsored study, Derick, et al., report that all concentrations which includes the .08 of brimonidine significantly reduced IOP from baseline. Is that accurate?

A. **That is accurate.**

Q. **And then in 1999, a couple years later, they claim a therapeutically effective aqueous composition. Is that right?**

A. **That's Claim 1.**

Q. **Let's go back to just the Derick article. DTX-111.**

If we could look at Page 133, the next page, Table 2. Dr. Tanna, what is Table 2?

A. **Table 2 describes the intraocular pressure at various followup visits. Again, it's the mean, it's the average of all the patients who are in the study, at various followup visits that occurred during the treatment period. That is the first day after initiation of therapy, day 7, day 14, day 21, and day 28, which is as far as they went, and it reports it separately for each of the different concentrations of brimonidine tested. And it reports it as a percent reduction from baseline in the intraocular pressure.**

I should point out, by the way, that this is what we call the trough pressure. It's just before the next dose is to be administered.

Q. **Is the trough pressure an important measure in glaucoma medications?**

A. **I believe it is, yes.**

Q. **This chart reports five different days of visit. It provides information for them. Which one to you is the most**

important of those five numbers?

A. So, the vast majority of patients for whom I prescribe brimonidine, I am prescribing it for chronic, long-term use. In light of that, the most important, to me, is day 28, because that's the longest duration information that we have, at least from this particular paper.

Q. You sometimes prescribe glaucoma medication for years. Is that correct?

A. That's correct.

Q. What is the Derick article in 1997 reporting about the effectiveness of .08 compared to .2 percent?

A. It reports that there is a 13.2 percent reduction from baseline at the morning hour, the 8:00 a.m. pressure, just prior to installation of the next dose, again, 13.2 percent reduction in the .08 group, and a 15.5 percent reduction in the .2 group, and then it goes on to report also, I think it's important, 13.8 percent in the .5 percent group.

Q. The .08 -- it's not quite as good as the .2, is it?

A. It's not quite as good. But it's indistinguishable, certainly, from the .5. And whether there is a statistically significant difference at this time point, between the .08 and the .2 group, I am fairly certain that the paper specifically says that there were no significant differences at this time point.

Q. Now, Allergan is arguing that their inventions are

good because it allows the formulation at an effective amount for .15 percent. They brought the concentration from .2 percent to .15. Can you do a little circle where the .15 would be here, theoretically, if it existed?

A. **It does not exist. But if it did -- well, it didn't go exactly where I put it.**

I will try it again. It's in there. (Indicating.)

Q. **So somewhere in there. Would the .15 have been effective as the .2 percent?**

A. **We have no way of knowing from this study.**

Q. **Did Allergan ever test, to your knowledge, .15 percent in the original Alphagan formulation to see if they could have just reduced the concentration without any of these other changes?**

A. **Of all the documents I have seen, of all the papers I have seen published and so on, I have never seen the original formulation at 0.15 percent tested in humans.**

Q. **Allergan has argued that the allergy of brimonidine, that they find with Alphagan, is associated with the concentration of brimonidine.**

Would a reduction to a .15 percent in the original Alphagan vehicle potentially have given you a reduction in allergy?

A. **Yes. There is every reason to believe that based on**

this paper and other prior art publications.
Q. And in this paper, it's because it's a dose-related, they find that adverse events are dose-related. Is that fair to say?
A. That's correct.
Q. So you would expect that if it was a .15 percent, that it would have less allergy?
A. I would expect that to be the case.
Q. And based on this report, it could have comparable efficacy at a .2 percent, but we just don't know?
A. There is every reason to believe that possibility given how effective even the .08 percent was at this time point.
Q. But Allergan never reformulated with a .15 percent. Is that accurate?
A. Not --
Q. .15 in the original Alphagan?
A. That's correct.
Q. And they never had a patent, it wouldn't behoove them because they didn't have patent protection for the .15 percent?
A. Correct.
MS. BROOKS: I object.
THE COURT: That is sustained.
BY MR. SODIKOFF:

Q. **If we could go back to JTX-100.**

THE COURT: Counsel, about how much more do you have?

MR. SODIKOFF: I probably have about 15 minutes.

THE COURT: Let's take our morning break.

(Recess taken.)

THE COURT: Please take your seats. Let's continue.

MR. SODIKOFF: Thank you, Your Honor.

BY MR. SODIKOFF:

Q. **Dr. Tanna, I think we wrapped up on what was known before 1999. Now I would like to turn to some of the clinical testing between the prior art Alphagan and the Alphagan P .15 formulation?**

Are you familiar with the Katz article?

A. **Yes, I am.**

Q. **If we can look at DTX-170.**

What is the Katz article?

A. **This was an article published in 2002 in the Journal of Glaucoma, which described the results of two major clinical trials that were conducted in parallel. Allergan's documents refer to them in 007 and 008, that looked at the pressure lowering effects and the safety of three different formulations of brimonidine.**

Those were the 0.2 percent brimonidine original

formulation, then there were two preserved with Purite, with Refresh Tears, and those were the 0.15 percent brimonidine and the 0.2 percent brimonidine, with Refresh.

Q. **I would like to focus on a comparison between the prior art Alphagan .2 percent and the Alphagan .15 percent peak, if that's okay?**

A. **Could you repeat that?**

Q. **Comparing the old formulation to the .15 peak?**

A. **Yes.**

Q. **If we look at Page 122 of Katz. This is in the middle talking about the efficacy of two drugs. Is that correct?**

A. **Correct.**

Q. **What does this relate about the efficacy of the prior art .2 percent with no Purite and the .15 percent brimonidine-Purite, which is the Alphagan P?**

A. **In a nutshell, that there were few statistically significant differences. It actually says there were no statistical significant differences in mean IOP. But at certain time points, there were differences favored the original formulation brimonidine 0.2 percent.**

Q. **Going back to your first statement, just to be really clear, what is it, after the comma in that sentence, what does that say?**

A. **It says, Except at the 5:00 p.m. time points at month three, and then it gives a "P" value which is less than 0.05**

which means it is statistically significant, that the difference was statistically significant.

Q. **So there was one difference in an IOP measurement between the brimonidine-Purite .15 percent and the brimonidine .2 percent?**

A. **That, in mean diameter IOP, which means the average of daytime pressure measurements that were taken.**

There were even more differences than that, if you parse it down more finely.

Q. **Can you explain that to me?**

A. **Yes. For example, I think I have it right here, it says, There were no statistically significant differences in the mean changes from baseline and dianol IOP measurements except for the 10:00 a.m. time point at week two, the 5:00 p.m. time point at month three, and the 5:00 p.m. time point at month six. All of those were statistically different. If I recall correctly, they all favored the higher concentration original formulation.**

Q. **Looking, again, at the first sentence, it says that, "Where there was a difference, it was in favor of the old formulation." Is that correct?**

A. **Yes.**

Q. **In this sentence, where it reports differences in efficacy, each time, while not statistically significant, they were in favor of the old brimonidine as well?**

A. **You mean the second half that I just read?**

Q. **Yeah.**

A. **It actually states that some of those differences were statistically significant.**

Q. **And those, all the differences, where there are differences, favor the old formulation of brimonidine?**

A. **That's my recollection. But let me make certain.**

Q. **Looking -- if we can do a split screen between 122 and 123.**

A. **Yes, that is correct. Whenever there was a difference in pressure lowering, the difference seemed to favor brimonidine 0.2 percent in the original formulation. But there were few differences.**

Q. **Is that reflected where it says respectively favoring brimonidine .2 percent?**

A. **Correct.**

Q. **What was your overall opinion regarding the efficacy of the old formulation brimonidine .2 percent, the Alphagan, the prior art formulation, and the current Alphagan .15 P?**

A. **In terms of efficacy?**

Q. **Yes.**

A. **I agree with the statement that's on the screen right now that says that there is comparable efficacy.**

Q. **Let's look -- would you expect there to be comparable efficacy in light of what we saw in the Derick article, that**

the .08 percent provided therapeutic benefits?

A. **Yes. There is a difference here. The formulation is different. This is brimonidine and Refresh Tears, whereas, that .08 that we were looking at before was brimonidine .08 percent in the original formulation. But given what we saw in Derick, I would not at all be surprised and I would actually expect this result, that there would be similar efficacy.**

Q. **And the reason you can't draw a conclusion, a firm conclusion, is because there is two variables that have been switched. Is that right?**

A. **That's right. That's exactly right.**

Q. **So, between Derick in here, the concentration in Derick was .08, and here, the Alphagan P is .15, but also the vehicle switched from the Derick article, where it was the prior art vehicle, and now it's this Purite vehicle. Correct?**

A. **That's correct.**

Q. **And you don't know where the efficacy similarity stems from, the difference in the concentration, or the difference in the vehicle?**

A. **That's exactly right. You can't tell for certain.**

Q. **Let's look at the safety of the Alphagan .2 percent to the Alphagan Purite referred here as brimonidine-Purite .15 percent.**

What would you expect regarding the safety just for the change in concentration?

A. **Well, they use the term "safety" here. First of all, I probably would take issue with the term "safety." I did a peer-review for a journal article recently where the term "safety review" for side effects were relatively mild. So I probably would prefer tolerability here but it is a minor point.**

Could you repeat your question, now that I have confused myself?

Q. **Sure.**

(Pending question read.)

A. **What would I expect?**

I would expect --

Q. **Let me just clear up that question. I don't know if it came out quite right.**

The original Alphagan was at .2 percent. Correct?

A. **That's correct.**

Q. **It's compared here -- that's the wrong page.**

It's compared in this article, you compare the old brimonidine .2 percent to the Alphagan P .15 percent. Correct?

A. **That's correct.**

Q. **And that lowers the concentration by .05 percent?**

A. **That's correct.**

Q. **What would you expect from lowering the concentration .05 percent for the brimonidine?**

A. **It's a general principle of pharmacology that the lower the concentration of a drug that you use, the lower the anticipated, the lower the severity and incidence of anticipated side effects. And that's supported for this particular drug by the Derick article, which showed this dose response relationship with adverse events.**

Q. **So Derick showed that the general principle of reducing concentration gets reduced side effects applies to brimonidine tartrate?**

A. **Exactly right.**

Q. **If we can look at Page 124, under "Quality of Life." Actually, if we can go to the first page of this article, just for one second.**

On the bottom left, it states here that this article was supported by Allergan. Is that correct?

A. **That is correct.**

Q. **And they are the plaintiff here?**

A. **They are the plaintiff.**

Q. **Do you have knowledge of whether -- strike that.**

If we can go to Page 124, under "Quality of Life," what does the first sentence here say?

A. **It says, "There were no statistical differences in the**

investigator's response to the clinical success of the medications."

Q. **And the investigator's response, who is the investigator?**

A. **At each of the sites, there is really two multi-center studies pooled together, at each of the numerous sites, there are clinician investigators. Those are the people who are actually doing the evaluation of the patients, filling out data forms, sending information back through clerical assistants, information back to the sponsor, in this case, Allergan.**

Q. **Is this response, does it reflect what a doctor thought about the clinical success? Is that what this is trying to embody?**

A. **Exactly. I am referring to ophthalmologists, almost all of whom, I believe, were glaucoma specialists.**

Q. **When you say "the investigator," that is an ophthalmologist in the field?**

A. **That's right.**

Q. **What did they say about the quality of life in the Alphagan .2 percent compared to the Alphagan P .15 percent?**

A. **Well, we don't have a lot of details in terms of how it was measured and what the actual numbers were. But at least the author's summary statement here, and presumably he did a statistical analysis, Dr. Katz, states that there was**

no statistical difference in the investigator's response to the clinical success of the medications.

Q. **I think you raise an interesting point. The sentence that says that the treatments between -- this basically -- let me start this over.**

Does this sentence basically state that the Alphagan prior art .2 percent and the Alphagan P .15 percent were the same, at least for this measurement?

A. **That is my interpretation of what it says. I am fairly certain that that is what the author intended to report here.**

By the way, I should point out, in case I didn't make this clear when you asked me before, it is not as if investigators were asked, just, you know, in a general way, Was original formulation Alphagan as effective as the new formulations being tested? But, per patient, there would have been a question, Was this clinically successful?

That data, across all the patients, would have been statistically analyzed.

Q. **The data showing that the two formulations, the prior art and the current one, are similar safety, that is reflected in one sentence here. Is that correct?**

A. **I am sorry. Which sentence?**

Q. **The same sentence we have been looking at. There were no statistical differences, the very first sentence of this**

paragraph.

A. **It says "clinical success." So that would take safety into account. For example, if a patient had an adverse event that required that they stop using the drug, that would not be a clinical success.**

Q. **Just based on the page, this is one sentence. Is that right?**

A. **This is one sentence.**

Q. **And then, now we go into the next sentence, which talks about patient, differences in patients, how they rated their satisfaction, and there is a difference there between the brimonidine .2 percent and the brimonidine-Purite, the new one, .15 percent. Is that correct?**

A. **Correct. There is a difference between what's now called Alphagan P 0.15 percent and the original formulation of brimonidine.**

Q. **When there is a difference, now, all of a sudden, we are getting all the data and all the statistics and a lot of analysis about differences where it shows that Alphagan P is a little better for this specific parameter. Is that fair to say, looking at this article? If we can look at the whole page.**

A. **In general, that seems correct about this article.**

Q. **And Allergan was the sponsor of this article?**

A. **Correct.**

Q. **Let's look at Table 2 on the top. This seems to be the major focus of Allergan. Can you tell us what this tells us about the rate of allergy in the different medications?**

A. **The allergic conjunctivitis rate is listed there. It is the first item listed, under "Adverse event." It shows that the percent incidence of allergy in the brimonidine-Purite 0.15 percent group, that is the marketed Alphagan P, is 9.2 percent. In the brimonidine-Purite 0.2 percent group, which was never marketed, was that means is, is there a statistically significant difference among those three? But it doesn't tell you -- it doesn't look specifically and answer the question, Where does that difference exist?**

So the next column looks specifically for a statistically significant difference between Alphagan P 0.15 percent, brimonidine-Purite 0.15 percent, and the original prior art version, Alphagan .2 percent.

The conjunctivitis, if I may finish, it says that that P value is 0.007 percent, which means there is a statistically significant difference between that pair.

Q. **I believe you stated that before 1999, you treated patients with the old Alphagan. Is that correct?**

A. **That's correct, because that's all we had before 1999, as far as brimonidine goes.**

Q. **And then eventually Allergan started marketing Alphagan P .15 percent?**

A. **Yes.**

Q. **And they withdrew from the market before the generic was available, the brimonidine .2 percent. Is that correct?**

A. **Prior to the loss of their exclusivity and prior, of course, to the availability of the generic, correct.**

Q. **Did you have patients that you were treating with Alphagan and then you moved them on to the new Alphagan P .15 percent?**

A. **Yes. I had a lot of patients who were on original formulation Alphagan when the new product became available.**

Q. **What is your opinion about the differences, if any, that you saw in patients between these treatments?**

A. **I will say I had to switch, because, again, the original formulation suddenly became unavailable. And I did not observe a difference that I was able to detect in the routine care of patients.**

Q. **Does that mean that the statistical difference doesn't exist?**

A. **No. I didn't say that this doesn't exist. I just didn't detect the difference. The differences were subtle enough that, without formally studying it, I don't think it could be detected.**

Q. **What is the purpose of having statistical analysis in**

a document like this?

A. **The purpose is to get to the question, really, in a pure statistical sense, what you are trying to answer is the question, What is the likelihood that this difference occurred as a result of chance alone? And the corollary to that is, What is the likelihood that this difference is due to some real difference between the two drugs?**

Q. **Does statistical analysis try to get rid of what I will refer to as "biases"?**

A. **Right. Whenever you are doing a formal study in which you are doing statistical analyses, when you are prospectively gathering data in a methodical way, that eliminates a lot of the bias that would be present when a clinician, in the course of taking care of patients, would try and think about what the occurrence is of certain side effects, because there is something called recall bias in which we remember the worst case scenarios and those stick in our minds, and then we can get a sense that there is a difference sometimes when there really isn't.**

Q. **You mentioned worst case scenario. I would like to take a look at ADX-7.**

Dr. Tanna, how long have you been treating patients with glaucoma?

A. **Since July, 1995.**

Q. **Approximately how many patients have you seen from**

that time till today?

A. **Well, I did calculate for you that in the past ten years while I have been at Northwestern, I think I have seen about 50,000 visits.**

Q. **Have you ever seen a patient present an allergic conjunctivitis reaction like this from a brimonidine product?**

A. **I have never seen anything quite that bad from brimonidine. I would say during the entire time I have practiced ophthalmology, including as a resident, so going back to 1995, I have seen maybe two or three people with allergic conjunctivitis that terrible. I don't think any of them had an allergic response to brimonidine.**

Actually, I take that back. I think, more accurately, those cases that I saw, they were viral conjunctivitis that looked that bad, infectious conjunctivitis.

Q. **So this ADX-7, this shocking picture, isn't a typical case of allergic conjunctivitis. Is that fair to say?**

A. **This is as atypical as they get.**

Q. **What do you do if a patient presents with an allergy to brimonidine?**

A. **Discontinue the brimonidine.**

Q. **And what happens then?**

A. **It depends on what other medications the patient had**

been on. Sometimes --

Q. **What happens to the allergy then?**

A. **The allergy symptoms and signs go away typically over the course of the next couple weeks.**

Q. **Is there any long-term damage, typically, from an allergy to brimonidine?**

A. **No, not typically.**

MR. SODIKOFF: Thank you, Your Honor. I am done.

THE COURT: You are welcome, counsel.

Ms. Brooks.

MS. BROOKS: Thank you, Your Honor.

THE COURT: You may cross.

CROSS-EXAMINATION

BY MS. BROOKS:

Q. **Hello, Dr. Tanna. My name is Juanita Brooks. I don't believe we have ever met.**

A. **Good morning, Ms. Brooks.**

Q. **Dr. Tanna, I want to ask you just one question about your very last point regarding the allergic reaction to brimonidine. You were asked what happens as far as the allergy, and you said that it essentially resolves itself.**

A. **That's correct --**

Q. **But --**

A. **-- once the offending agent is discontinued.**

Q. **But once a patient presents with allergic conjunctivitis as a result of the brimonidine, are you essentially prevented from re-prescribing the brimonidine, once they develop that sensitivity?**

A. **Well, prevented, I don't know about prevented. There have been a couple times, you know, within the past month that I have used brimonidine as a single dose in a patient who is known to have a brimonidine allergy because we were about to do laser surgery and brimonidine is very effective at preventing an adverse event that can occur after laser surgery in which the pressure can spike for a day or two.**

So I have used brimonidine occasionally in people known to have a brimonidine allergy. But for chronic use in someone who is known to have a brimonidine allergy, you certainly wouldn't do it.

Q. **That is what I meant to ask.**

You certainly, as a physician, once an individual has presented with an allergy as a result of brimonidine, aren't going to prescribe it again for the treatment, for example, of glaucoma?

A. **Correct. You wouldn't use a medication that a person is allergic to, knowing it.**

Q. **That then takes one weapon out of your arsenal in your fight against glaucoma?**

A. **That's correct.**

Q. **Now, let's go back to some of your earlier opinions. You gave us some opinions regarding what would or would not have been obvious to one of skill in the art. Do you recall that?**

A. **Yes, I do.**

Q. **And in your expert report, when you said, you referred to the term one of skill in the art, you didn't give a definition as to whom you believed one of skill in the art would be.**

A. **I accepted Dr. Gil Banker's definition in my expert opinion report, expert report.**

But when I was deposed by Mr. Shear, I acknowledged that Dr. Gil had a different definition, and that I didn't think that the two were very different and I didn't have any problem with agreeing to Dr. Gil's.

Q. **To either one?**

A. **Correct.**

Q. **I think, when you say "Dr. Gil," are you sure you don't mean Dr. Stella?**

A. **I thought it was Dr. Gil who described the Allergan point of view of what an expert -- I am sorry, of what one skilled in the art is. But I may be remembering incorrectly.**

Q. **That is fine.**

Let's take, then, for the purpose of your

testimony, the definition of whom one of skill in the art is from Dr. Banker, Apotex's expert, since that's the one you relied upon when you wrote your report.

A. Yes.

Q. Okay. If I could have the binders for you?

MS. BROOKS: If I might approach the witness, Your Honor?

THE COURT: Yes, you may.

MS. BROOKS: Thank you. I do have an extra copy, yet another copy, Your Honor, if the Court would like?

THE COURT: You have another copy?

MS. BROOKS: Yes, I do.

BY MS. BROOKS:

Q. Dr. Tanna, in your binder should be -- I didn't want to put all of Dr. Banker's report in there because it's pretty thick. But I did put in Pages 6, 7, and 8, where he discusses whom one of skill in the art would be. He begins on Page 6, where you see the Subsection (b), relevant prior art and persons of ordinary skill in the art. Do you see that?

A. Yes, Section 17 I think is where it starts.

Q. Then he, first of all, refers to the '078 patent. That is the patent in this case that deals with Purite. I take it you are not here to render any kind of opinion regarding that particular patent?

A. **Well, I have reviewed the patent carefully. I do have an understanding of how Purite works. And, so, if you ask me -- I don't think that I have said anything pertaining to the '078 patent yet.**

Q. **Okay. Then, if we go to the next series of patents, the '873, the '210, the '834, and the '337, that definition of one of skill in the art begins at Paragraph 19. First of all, Dr. Banker says that a person having ordinary skill in the art with respect to the subject matter of the '210, '337, '834, and '873 patents, would have at least a doctorate degree in pharmacy, pharmacology, or pharmaceutical sciences, and at least two years' experience.**

Let me stop right there, Dr. Tanna. You don't meet that definition of, Dr. Banker's definition of one of skill in the art. Is that correct?

A. **That's correct.**

Q. **He goes on to say, "Or a Bachelor of Science or Pharm D, Doctor of Pharmacy Degree, and an additional two to three years' experience developing ophthalmic pharmaceutical compositions such as ophthalmic ointments and eyedrops containing pharmaceutically active ingredients."**

I take it, Dr. Tanna, you don't meet that definition of Dr. Banker's definition of one of skill in the art?

A. **That's correct.**

Q. **Then he goes on to say, there is yet a third category, "If a worker's formal education is not in the pharmaceutical sciences or pharmacology, per se, but in a related field, such as chemistry, to be one of ordinary skill in the art would require such an individual to have several additional years of actual experience formulating, developing, and/or using such products."**

I take it you don't meet that definition, either?

A. **You are correct.**

Q. **In fact, in Paragraph 20, he goes on to describe what he means by that experience. He gives, for example, in the middle of that paragraph, that the person's experience would include pre-formulation and formulation activities relating to the development of aqueous ophthalmic products, including familiarity with common strategies for optimizing ophthalmic formulations and improving stability.**

And, again, I take it, Dr. Tanna, based on what you have told us, you do not meet that definition of Dr. Banker's definition of one of skill in the art?

A. **Correct.**

Q. **And, in fact, you were very candid with us at your deposition that you have no experience in formulating ophthalmic products?**

A. **Correct. I only have experience in offering advice as**

to formulating ophthalmic products to drug companies who seek that advice.

Q. While, again, you offer advice when you were asked about how particular products were formulated, you said, That's not my area of expertise as to how products are formulated.

Did I get that correctly?

A. The actual chemistry, that's correct, I don't do the actual chemistry.

Q. In fact, you were asked about certain compositions of various glaucoma medications and whether they were ionic or not. And you said, I can't speak to that, I don't formulate.

A. That's correct.

Q. Now, you understand, Dr. Tanna, that there is a reason why, in the world of patent law, one has to look at the patents through the eyes of one of skill in the art?

MR. SODIKOFF: Objection, Your Honor. That calls for a legal conclusion.

THE COURT: You can rephrase that, Ms. Brooks.

MS. BROOKS: Thank you.

BY MS. BROOKS:

Q. Dr. Tanna, do you understand that in rendering an opinion as to what would or would not have been obvious, what must go into that opinion is what would or would not

have been obvious to one of skill in the art?

MR. SODIKOFF: Objection, Your Honor.

THE COURT: If he understands it, go ahead.

BY MS. BROOKS:

Q. **Do you have that understanding, Dr. Tanna?**

A. **Could you repeat it, please?**

Q. **Sure. You understand, do you not, sir, in fact, you put it in your expert report, that in viewing whether something would or would not have been obvious, one views it from the perspective of one of skill in the art?**

A. **Yes. I was advised by counsel that, in answering those questions, I had to view it as one of ordinary skill in the art as defined by Dr. Banker, not as myself.**

Q. **Excellent. Okay.**

And do you understand the purpose of that is because, for example, something that might seem very complicated to me, a layperson, to one of skill in the art, might be obvious, based on all the knowledge that they have from their years of experience?

MR. SODIKOFF: Objection, Your Honor.

THE COURT: Overruled.

BY MS. BROOKS:

Q. **Do you understand that, Dr. Tanna?**

A. **Would you repeat that, please?**

MS. BROOKS: I will ask to have it read back.

(Pending question read.)

THE WITNESS: Yes, I agree with that.

BY MS. BROOKS:

Q. **In fact, the reverse might be true, which is something that may seem obvious to me, a layperson, like why don't you just take brimonidine and put it in an artificial tear, may not be obvious at all to one of skill in the art because they know that formulation is much more complicated than that. You understand that, too?**

A. **Well, I hear what you said. But I don't really agree with that.**

Q. **So you don't agree that what should be taken into consideration, in determining what would be obvious or not to a formulator, you don't agree that what should be taken into consideration is the knowledge of the formulator?**

A. **I agree that that should be taken into consideration. What I am at issue with, and I do not really agree with, is this idea that somehow having this special knowledge can lead to one being unable to see something obvious to a layperson. I don't agree with that. I don't really see how that would happen.**

Q. **Let me ask you this: If it seemed obvious to a layperson to simply take Purite, for example, and combine it with brimonidine but one of skill in the art would know that the Purite might oxidize the brimonidine, isn't that a**

factor we should take into consideration?

A. **Well, there is data in the literature that brimonidine is resistant to oxidation. So I don't agree with that particular example.**

Q. **My question, sir, was: If a formulator believes -- well, you said there is data in the literature that brimonidine itself is -- what was the word?**

A. **I said "resistant." But I should say relatively resistant to oxidation.**

Q. **Relatively resistant to oxidation. Do you know the makeup of Purite?**

A. **I do.**

Q. **That, in fact, it is an oxychloro?**

A. **Well, it's a sodium chlorite solution, which exists in three different species, sodium chlorite, sodium chlorate and chlorine dioxide as very, very low concentrations, I am familiar with that. And I am familiar with the idea that the way chlorine dioxide works is as an oxidizing agent.**

Q. **If we look at JTX-044, which was used with Dr. Kerslake, if it is not up there in front of you, I will hand you my copy or we can put it on the screen.**

MR. SODIKOFF: I don't have a copy, Your Honor.

MS. BROOKS: Counsel just used it with Dr. Kerslake.

If I can approach the witness and give him my

copy.

MR. SODIKOFF: So he can see the whole document.

THE WITNESS: It's a one-page -- I see. There are more pages here.

BY MS. BROOKS:

Q. **Dr. Tanna, can you see, right under "Recommendations," the first bullet point, where the second sentence talks about the issue will be the stability of the formulation due to potential for drug oxidation?**

Do you see that?

A. **I certainly see it. But there was prior art data that showed that brimonidine is relatively resistant to oxidation. So, although, because you are using an oxidizing agent as a preservative, you have to be thinking about it, I believe one of ordinary skill would be motivated to try it and would have a reasonable expectation of success.**

Q. **Now, Dr. Tanna, we have already established, you are not one of ordinary skill. Correct?**

A. **I agree with that as defined by Dr. Banker.**

Q. **Thank you.**

A. **But, nevertheless, I have read this information and I am aware of it, so, in order to completely answer your question, I had to make that statement that I just made.**

Q. **But, Dr. Tanna, my question was actually quite simple: You are not one of ordinary skill. Correct?**

A. **That's correct, based on Dr. Banker's definition.**

Q. **Thank you.**

Were you here for the testimony of Dr. Olejnik?

A. **Yes, I did hear Dr. Olejnik's testimony.**

Q. **You heard his vast, decades and decades of experience working in ophthalmic formulations?**

A. **Yes, I did.**

Q. **And you heard the testimony of Dr. Kerslake?**

A. **I did.**

Q. **And you heard Dr. Kerslake, while having been out of the science for 12 years, at the time of these formulations, having a Ph.D. in this area and having been a formulator for quite some time?**

A. **I am aware that he was from the testimony I heard, correct.**

Q. **You heard the expression of these two gentlemen that they were not only concerned with whether or not the Purite might oxidize the brimonidine, but whether or not the Purite itself, in combination with an active ingredient might become unstable?**

MR. SODIKOFF: Objection, Your Honor. This is argumentative. The record is what the record is.

THE COURT: No, no. This is cross-examination, counsel.

BY MS. BROOKS:

Q. **You heard them testify to that, did you not, sir?**

A. **I did hear that.**

Q. **Again, that was their concerns as formulators at the time?**

A. **That's what they stated.**

Q. **In combing --**

A. **That's what -- you know, I don't know, the recollections were incomplete and so on. I don't know that Dr. Kerslake actually stated that that was a concern of his at the time. I don't think he remembered a lot of what occurred at the time. And I did hear Dr. Olejnik say very clearly that that was a concern of his at the time.**

Q. **Thank you.**

In addition to that, you heard the concerns of Dr. Olejnik, at least, let's stick with Dr. Olejnik, that brimonidine, if it is formulated at higher pH's, has solubility problems?

A. **He stated that that was a concern of his.**

Q. **And, in fact, the actual solubility studies reflecting how the solubility of brimonidine is pH dependent were actually put into the patents that Dr. Olejnik showed the Court?**

A. **They were. But I don't completely agree with the interpretation that's been discussed.**

Q. **But you, yourself, admit that you are not one of skill**

in the art. Is that correct?

A. **I am not one of skill in the art as defined by Dr. Banker.**

Q. **Let's go to something you can tell us about, though.**

You told us that it is known, and I believe you went through several, several papers about how BAK, benzoalkonium chloride, can be hard on the eye?

A. **I think that I used the term that it has ocular surface toxicity. I think, more precisely, to say it accurately, would be that there is ocular surface toxicity associated with the use of benzoalkonium chloride and that benzoalkonium chloride has a proinflammatory effect on the surface of the eye.**

Q. **I want to get your words exactly. I tried to shorthand it with "hard on the eye." Ocular surface toxicity?**

A. **Correct.**

Q. **What was the next one?**

A. **A proinflammatory effect on the ocular surface.**

Q. **Proinflammatory effect?**

A. **Yes.**

Q. **And were there any more?**

A. **Well, we know that it induces fibroblast proliferation, so the scar tissue story as it pertains to glaucoma surgery.**

We also no that it destabilizes the tear film and can exacerbate the symptoms of dry eye.

Q. **We have ocular surface toxicity, pro-inflammatory, fibroblast proliferation, destabilizes the other --**

A. **Destabilizes the tear film and thereby can exacerbate the symptoms of dry eye.**

Q. **Okay, great.**

That was known. Right? You showed us paper after paper how those sort of phenomena were discussed out there in the field?

A. **That's correct.**

Q. **So you have got all these formulators sitting around back at their various ophthalmic companies knowing that BAK could, in fact, have ocular surface toxicity, proinflammatory effect, fibroblast proliferation and destabilization of tear film?**

A. **While at the same time knowing that the majority of products had benzoalkonium chloride and it was reasonably well tolerated, people's eyes were not falling out of their heads, but that there would be a benefit to come up with a gentler preservative.**

Q. **Absolutely.**

A. **Yes.**

Q. **They knew that, they thought, you know what? If I can just substitute this BAK with a gentler preservative, I am**

going to make for my company a better product. Right?

A. **I believe that people were thinking along those lines prior to July '99.**

Q. **And that certainly would have been in their minds, you said, prior to July '99. Is that right?**

A. **That's correct.**

Q. **I would like to go back and talk a little bit about the various glaucoma medications that are on the market that you, yourself, use.**

A. **Yes.**

Q. **I believe you mentioned some of them.**

The leading one, is that Xalatan? Is that the leading glaucoma medication?

A. **That is the most commonly prescribed glaucoma medication in the United States today.**

Q. **It has been out there for quite some time. Is that right?**

A. **I believe '96.**

Q. **It's manufactured by Pharmacia?**

A. **Pharmacia does not exist. It is now manufactured by Pfizer.**

Q. **Pfizer. So one of those mergers. Now we have got Pfizer manufacturing Xalatan. Is that right?**

A. **That's correct.**

Q. **Xalatan has BAK in it, does it not?**

A. **It does.**
Q. **And has had since 1996?**
A. **Yes. There have been no formulation changes since it was first FDA-approved and marketed.**
Q. **So your answer, sir, is yes?**
A. **Correct.**
Q. **Trusopt, that is another glaucoma medication. Correct?**
A. **Correct.**
Q. **And that has BAK in it, does it not?**
A. **Yes, it does.**
Q. **And Timoptic, that is another glaucoma medication?**
A. **That is.**
Q. **And that has BAK in it, does it not?**
A. **It's available in multiple formulations and there is a formulation available with no preservative. It's called Timoptic Ocudose.**
Q. **So preservative-free glaucoma medications, first of all, those can only be unit-dose medications. Is that right?**
A. **That's correct.**
Q. **You can't use it chronically over time?**
A. **There is a preservative-free multiple-dose ophthalmic medication.**
Q. **And how does that work? You have to do it one dose at**

a time and it seals back up?

A. **No, the active ingredient --**

THE COURT: As interesting as that is, counsel --

MS. BROOKS: It is totally irrelevant. So I will move on.

BY MS. BROOKS:

Q. **Let's stick with the glaucoma medications that have preservatives in them.**

A. **Sure.**

Q. **So we have already covered Xalatan has BAK. Correct?**

A. **That's correct.**

Q. **Trusopt has BAK?**

A. **That's correct.**

Q. **Timoptic has BAK?**

A. **That's correct.**

Q. **Rescula, is that another glaucoma medication?**

A. **Rescula is no longer marketed in the United States.**

Q. **We will take that one off our chart. Lumigan has BAK?**

A. **Yes, it.**

Q. **Cosopt has BAK?**

A. **That's correct.**

Q. **Betoptic, is that still on the market?**

A. **It is.**

Q. **Does that have BAK?**

A. **It does.**
Q. **Betagan has BAK?**
A. **Correct.**
Q. **And Azopt has BAK?**
A. **Correct.**
Q. **And the original Alphagan had BAK?**
A. **Correct.**
Q. **In fact, of the leading glaucoma medications, the only two where the formulators were able to substitute BAK with a more gentle preservative was Alphagan P. Correct?**
A. **That's correct.**
Q. **And Travatan Z?**
A. **That's correct. Well, there is another one out there and it's dodecynium (phonetic) bromide. But it is pretty similar in terms of toxicity. It is thought to be less toxic, but I don't think there is a big difference at all.**
Q. **So while they try to substitute in that case, the one you just told us about, they tried to substitute a more gentle preservative, apparently, it didn't work?**
A. **It was an alternate preservative. It worked, it's commercially available. It's called dodecynium (phonetic) bromide. That is the preservative.**
Q. **But of the, all the leading glaucoma medications that we have just talked about, the only two where formulators were able to do what made perfect sense, which was**

substitute BAK for a more gentle preservative, was in the case of Alphagan P and Travatan Z?

A. **In a meaningful way in terms of the difference, yes, I agree with that.**

Q. **Thank you.**

And Travatan Z, is that a line extension by Alcon of the original Travatan?

A. **My understanding is it did not result in additional patent protection. That's my understanding. But I am not a lawyer and I do not know the details of whether that's the case.**

I did ask fairly senior people at Alcon that particular question. And my understanding in that response is that there was no change in exclusivity.

Q. **Are you aware, sir, that there are four listed patents for Travatan Z in the Orange Book?**

A. **I am not aware of that.**

Q. **Okay. Thank you.**

Now, in addition to all these other companies, the makers of Xalatan and Trusopt and Betagan and Timoptic, not being able to substitute BAK with a more gentle preservative, I would like to show you what was shown in opening statement --

MR. SODIKOFF: Objection, Your Honor.

THE COURT: She hasn't finished the question,

counsel.

MR. SODIKOFF: I think she is mischaracterizing the testimony.

THE COURT: She is just talking about showing him something.

BY MS. BROOKS:

Q. **I would like to show you what was put up in opening statement by Exela as to what their formulation of Alphagan P is going to be. And it was opening Slide 23.**

MR. SODIKOFF: Your Honor, I object. That is outside the scope of both direct and his expert report. We didn't even have Exela's formulation during discovery.

MS. BROOKS: Your Honor, this is just cross-examination to establish yet there is another proposed, at least, formulation that is going to obtain BAK yet again.

MR. SODIKOFF: Your Honor, we heard Mr. Boggs say the whole point of that was to try to avoid patent infringement. It wasn't scientifically based. I don't think it is really relevant to what we are talking about here.

THE COURT: What about his first basis, it sounds like it might be outside the scope of the direct examination?

MS. BROOKS: I thought we dealt significantly on

direct about BAK and how one would have been motivated to replace it with a more gentle preservative. I am just trying to show the Court all the examples where formulators either weren't motivated to do so or were unable to do so, one of two things.

THE COURT: All right.

BY MS. BROOKS:

Q. Sir, I just wanted to show you what is put up as Slide 23 in Exela's opening. It appears that Exela is, if they ever do get FDA approval, going to use BAK as their preservative in what would be a generic Alphagan P?

THE COURT: What has been done and what might be done, I think, there is a difference.

I am going to reverse myself. I am going to sustain this objection.

MS. BROOKS: Fine, Your Honor. Thank you. I will move on.

BY MS. BROOKS:

Q. Now, in addition to one wanting to substitute BAK for a more gentle preservative, I believe you said that it was also a good idea to try to have the ophthalmic medication be as close to the pH of the eye as possible?

A. That's a general principle in formulating ophthalmic medications and in terms of what we want. It's not always possible. But it is, for example, the pH of Trusopt is 4.3,

very low. But that's because the molecule requires such a low pH to go into solution, at least that particular molecule, dorzolamide.

Q. **I think you answered my question.**

A. **It is desirable.**

Q. **You answered my question, thank you.**

Even the next one I was going to ask, which is, is it desirable? And apparently it is.

A. **It is desirable to attempt to formulate ophthalmic medications, eyedrops, at a pH and other physical characteristics as close to the ocular tear film as possible, in general.**

Q. **And that, again, was a well-known concept out in the industry. Right?**

A. **Right.**

Q. **And, yet, despite that, there were many, many formulations that were unable to do that. Correct?**

A. **Correct.**

Q. **For example, Trusopt, is that a 4.5 pH?**

A. **I thought 4.3, offhand. I could be mistaken. You have it in front of you. I haven't looked at it in a couple years, probably.**

Q. **Actually, it is my handwriting I can't read. Maybe it is 4.3.**

All we know is it is on the acidic end of the pH

scale?

A. **That's correct.**

Q. **It is out there being sold right now as a glaucoma medication?**

A. **Correct.**

Q. **For whatever reasons, the manufacturers of Trusopt were either unable or unwilling to formulate that drug at a higher pH?**

A. **In that case, it was because they were unable to do it.**

Q. **Unable to do it. Would they have to overcome some form of obstacle in order to formulate that drug at a higher pH?**

A. **It just couldn't be done. A different company had to go to an entirely different molecule and put it into suspension in order to achieve that class of medication at a higher pH. But there was motivation there to do it.**

Q. **But they were unable to?**

A. **Well, they kind of went around it by taking a different molecule and putting it into suspension. So there was motivation for another company to improve upon it and they did.**

Q. **So if one can't keep a particular molecule, active ingredient, in solution at a higher pH, one way to go around it or attempt to go around it would be to use a suspension.**

Correct?

A. **That's correct.**

Q. **And it wouldn't necessarily be obvious at all that you could do something else to it that would enable you to make a solution with that same active ingredient. Correct?**

A. **Well, brimonidine 0.2 percent was in solution.**

Q. **Exactly.**

A. **I am not sure I understand the problem.**

Q. **Exactly. Brimonidine .2 percent was in solution, was it not?**

A. **It was.**

Q. **It wasn't a suspension?**

A. **Correct.**

Q. **But it wasn't at a pH close to the pH of the eye, was it?**

A. **Well, it was close. It was 6.3, 6.5, somewhere in that range. That's pretty close. That is not 7.4, but it's close.**

Q. **It was at a pH on the acid end of the pH scale, was it not?**

A. **That's correct. But it was close. I don't think I would say it was far away from a physiologic pH.**

Q. **I am sorry, I didn't think I said "far away."**

Let's make sure we are having the same terminology. Neutral on a pH scale of 7?

A. **Correct.**

Q. **The pH of the eye is approximately 7.4?**

A. **The pH of the tear film.**

Q. **Thank you. I want to be precise. The pH of the tear film is approximately 7.4?**

A. **Correct.**

Q. **And the original Alphagan was at about 6.3 to 6.4 pH. Correct?**

A. **That's correct.**

Q. **Now, Alphagan P is at a pH of approximately 7.2?**

A. **Correct.**

Q. **And Alphagan P .1 percent is at a pH of approximately 7.7?**

A. **Correct.**

Q. **And Alphagan P and Alphagan P .1 percent came out as a result of the reformulation efforts that we have heard Dr. Olejnik and Dr. Kerslake testify about. Correct?**

A. **Correct.**

Q. **Now, you mentioned that you have patients that originally you had prescribed Alphagan to, and that you also suggested to your patients that they use Refresh Tears. Do you remember that testimony?**

A. **I do, yes.**

Q. **And you said that when they did that, when they used the Alphagan medication and they used the Refresh Tears**

medication, that they didn't seem to have any problems with it?

A. **Correct.**

Q. **Did you recommend to your patients that they attempt to take the Alphagan formulation and literally mix it into the Refresh Tears formulation and shake it up and leave it on their shelf and try to use it in that fashion?**

A. **No, I did not.**

Q. **I take it you didn't recommend them to do that because you didn't know what the results of such a formulation as that would be?**

A. **No. I didn't recommend it because it would be ludicrous to recommend such a thing, in general.**

Q. **Of course, it would.**

Now, are you aware -- you mentioned that a lot of glaucoma patients also suffer from dry eye. Do you recall that?

A. **Yes.**

Q. **Are you aware that the original Alphagan was in a vehicle called Liquifilm Tears, which was actually an artificial tear product?**

A. **Yes, I do remember. An older generation Allergan artificial tear product, I believe.**

Q. **Now, you mentioned, you were asked a question: Is there anything that would dissuade one to combine**

brimonidine and Refresh Tears. Do you remember that question?

A. **Yes, I do.**

Q. **And you answered no, there was nothing?**

A. **Correct.**

Q. **Correct?**

You answered that question not as one of skill in the art. Correct?

A. **That is correct.**

Q. **And, so, once again, you wouldn't be aware, as one not of skill in the art, what the concerns of one of skill in the art would be in making such a formulation?**

A. **I am aware of the general concepts of what the concern would be. I believe the question posed was, would I try it? And, yes, I would.**

Q. **But not as one of skill in the art?**

A. **Correct.**

Q. **Now let's go on to some of the papers that you went over with counsel. I am going to need to get the borrowed reading glasses from Dr. Olejnik here.**

You discussed for us DTX-063, which was part of a textbook called The Glaucomas. Do you recall that?

A. **I do.**

Q. **And, counsel, when direct-examining you, had you turn briefly to AGN 225387, which was the section on brimonidine.**

Do you recall being asked that?

A. **Yes, I do.**

Q. **I can't remember what part of this brimonidine section you referred to in your direct. Do you recall which part?**

A. **I was asked to read from the first paragraph, I believe.**

Q. **Okay. Let's, then, read from the third paragraph.**

This is a discussion about how brimonidine lowers intraocular pressure in various animal models over a dose range of .001 percent to 1 percent.

Do you see that?

A. **Yes.**

Q. **And then there is a citation 43, I assume that is a citation to the reference from which this statement came?**

A. **Yes.**

Q. **And then, before we get to the next sentence, just to put some background around this, you were asked questions about whether one should have known that you could treat, you could use the brimonidine at .15 percent. You were shown some studies where the study was done at .08 percent, .2 percent and .5 percent. Do you recall that?**

A. **Yes, I do.**

Q. **And you were asked whether, in looking at that data, one should have known that you could have actually made a therapeutically effective composition at .15 percent. Do**

you remember, you drew that circle in between the .08 and the .2?

A. Yes, I do.

Q. Let's look at what this reference actually says about that study.

"In a one-month dose-response study in humans, brimonidine .08 percent, .2 percent, and .5 percent, used twice daily, lowered pressure in open-angle glaucoma and ocular hypertensive patients, with a maximal pressure decrease between 20 percent and 30 percent."

Did I read that correctly?

A. You did. And can I just add right now, it pertains to earlier visits in the study than we were referring to.

Q. Okay. And we are going to get to those later papers and look at the later visits.

Let's look at what the author's conclusion is.

A. Here, the author, if I may interrupt --

Q. Actually, you can't.

A. The authors of the paper --

Q. Dr. Tanna, there needs to be a question pending, I am afraid.

A. I'm sorry.

Q. That's okay. I promise I won't interrupt you. But I need to pose the question. Okay?

A. Yes.

Q. **The authors concluded that brimonidine .2 percent appears to be the most effective dose, not only because it was at the top of the dose-response curve, but also because it had the fewest systemic and local side effects.**

Is that what the author's conclusion was that was in DTX-063 or at least is referenced in DTX-063?

A. **Again, what I was trying to say before is, just to make it clear to the Court, that, here, "authors" refers to the authors of the original study, which we looked at, and I would actually have to go to it to make sure, because I think that it's a mistake here, because it said that, also, it had the few systemic and local side effects, which we know is not true because the lowest systemic and local side effects were observed in the 0.08 percent brimonidine group, and I know when you write a textbook, you can make a mistake.**

Q. **All right. Let's go to the actual study, DTX-111. You should have that in front of you because I believe it was used by counsel.**

A. **I do have it.**

Q. **That is the Derick study?**

A. **Correct.**

Q. **Let's look at the "Results" section on the first page of the Derick study. And, specifically, in the middle, does it say right here, On days one and 21, so we are measuring**

two different days here, day one and day 21. Did I get that right?

A. **Correct.**

Q. **The .2 percent and the .5 percent treatment groups exhibited significantly greater IOP decreases than did the .08 percent group?**

Is that what Dr. Derick and his colleagues reported under the "Results" section of the study located at DTX-111?

A. **That is not exactly what they accurately reported. But it is what it states right here in their abstract.**

Q. **That's right there on the very front page. If one were wanting to get a quick analysis, we could look at "Results" and we could see this language verbatim under "Results" on that exhibit. Is that right?**

A. **But that would not be the way to get good information.**

Q. **Now, the way to get good information would probably be to look at the tables. Right?**

A. **To read the methods and results, I agree with what Dr. Olejnik said the other day, you have to look at the paper.**

Q. **Thank you. Dr. Olejnik, I am sure, will be happy to hear that.**

Let's go look at the tables. Specifically, let's start with Table 3.

Now, does Table 3 show us measures of the reduction of IOP on day one, day seven, day 14, day 21, and day 28?

A. **No, it doesn't show us the reduction of IOP. It tells us the proportion of -- actually, in this case, it is the number of individuals who achieved a certain threshold.**

Q. **Thank you. Okay. So it is actually showing us the number of individuals who achieved a certain threshold of IOP lowering. Is that right?**

A. **That's correct.**

Q. **Okay. And if we look here at day one, we have 12 individuals in the .08 percent group that reached that threshold. Correct?**

A. **That's correct.**

Q. **We have 23 individuals in the .2 percent group who reached that threshold. Correct?**

A. **Correct.**

Q. **And we have 38 individuals in the .5 percent group that reached that threshold?**

A. **Correct.**

Q. **Now, let's go to the halfway point. Let's look at Day 14. What have we got? Now we have got only eight individuals in the .08 percent group that have reached that threshold. Correct?**

A. **Correct.**

Q. **We have 15 individuals in the .2 percent group that has reached that threshold. Is that right?**

A. **Correct.**

Q. **Almost twice the number of people in the .08 group on day 14. Is that right?**

A. **Well, you say "almost twice." I say eight to 15, which is what the table says. It's close to twice.**

Q. **Twice would be 16?**

A. **Correct.**

Q. **So we are one percent short of twice?**

A. **Correct.**

Q. **Okay. And then 13 individuals who have reached -- what was the term again?**

A. **Well, it's a threshold value that they have selected among an infinite number of possible threshold values.**

Q. **Thirteen individuals who have reached the threshold value in the .5 percent group. Correct?**

A. **Correct.**

Q. **Okay. And then, if we go down to day 28, we have seven individuals who have reached the threshold value in the .08 percent group. Correct?**

A. **Correct.**

Q. **We have 15 individuals who have reached the threshold value in the .2 percent group. Correct?**

A. **Correct.**

Q. **And now, if I am doing my math correctly, we actually have twice as many individuals in the .2 percent group who have reached the threshold values on day 28 than those that reached the threshold values in the .8 percent group?**

A. **Correct. But at .5, only ten.**

Q. **Exactly. And as a result of that, this data right here where we only have -- we have less people reaching the threshold value in the .5 percent group, the authors, if we could go to the very last page in the paper on Page 135, which is Bates number 25142 right above "References," that paragraph right there, there we go, what the authors conclude is, "Because there appears to be no evidence to indicate that .5 percent is a more potent ocular hypotensive agent than the .2 percent, and because there are greater local and systemic side effects associated with the .5 percent concentration, brimonidine .2 percent appears to be the appropriate concentration for further long-term studies."**

Did I read that correctly?

A. **You read it correctly.**

Q. **Now, let's --**

A. **To me, no, that does not match what is stated in the book chapter from which you read a while ago.**

Q. **I thought the book chapter also said that .2 percent was the way to go?**

A. **No. I don't think that's what you showed me. I think that what you showed me said something different, actually.**

Q. **All right. Let's go back, if we could, to DTX-063 and specifically Bates number 225387. And down to the third paragraph, I am sorry, second column, third paragraph, Brimonidine lowers intraocular pressure, there we go.**

So what I had read to you was, the authors concluded that brimonidine .2 percent appears to be the most effective dose, then it goes on to say, not only because it was at the top of the dose response curve. Let me stop there.

You don't take issue with that, that first part?

A. **That the authors concluded that. They did conclude that.**

Q. **But also because it had the fewest systemic and local side effects. Is that the part you take issue with?**

A. **Correct. Because the previous sentence here suggests they are looking at all three. And the authors of the original paper, when they made the statement about going with .2, they were really comparing the side effects of .2 versus .5, and they didn't include .08.**

Q. **Excellent point, Dr. Tanna. Had they included .08, they would have seen yet additional reduced side effects in the .08 group, would they not?**

A. **That's correct.**

Q. **Less side effects in the .08 group than in the .2 percent group. Right?**

A. **Correct.**

Q. **So an enhanced safety profile in the .08 percent group?**

A. **Yes.**

Q. **But there was a tradeoff for that, was there not?**

A. **There was a tradeoff that impacted very dramatically the early study, day one, day seven, day 14 that I think you looked at, too. But at day 28, the differences were really very small.**

Q. **We will go back and look at those differences in a second. But the bottom line, Dr. Tanna, I think you actually mentioned this on direct, is it's not going to do a physician any good to get a better safety profile if the tradeoff is that the drug is less effective?**

A. **That's not necessarily true. A clinician has to take into account both efficacy and side effects. And he has to balance them in finding optimal balance for a particular patient.**

So, in fact, you may tradeoff some loss of efficacy in exchange for some benefit in terms of tolerability.

Q. **You certainly wouldn't be willing to trade off a significant loss of efficacy in exchange for better**

tolerability?

A. **Maybe you would. It depends on what you mean by "significant."**

Q. **Well, for example, let's go back to DTX -- I am looking for the Derick study, DTX-111, I believe. Let's go to that table we were looking at. If you can get twice as many patients, if we look at Day 28, twice as many patients meeting the threshold requirement on .2 percent than you did on .08 percent, then would you agree with the author's recommendations at the end of the Derick paper that .2 percent appeared to be the appropriate concentration for further long-term studies?**

A. **No, because this table is not how I judge efficacy of a drug. I don't judge efficacy solely or primarily based on some threshold reduction.**

I can explain why, if you wish.

Q. **That's okay. Since I am on the clock, you can explain it when they get up on redirect so it comes off their time. Okay?**

A. **Sure.**

Q. **But, just to be clear, the authors believed it was the correct conclusion. Correct?**

A. **The authors stated that .2 appears appropriate for further development. The authors were consultants to Allergan. I don't know what they really believed. And I**

don't know for sure that, with all the data in hand, they truly felt that .08 was not worth pursuing. I don't know that.

Q. Well, we know that Alphagan came out at .2 percent?

A. I think that they were on a .2 railroad track at this point.

Q. My question, sir, was we know that Alphagan came out at .2 percent. Correct?

A. I thought it was a statement. But, yes.

Q. I can't remember, Dr. Tanna, did you talk about DTX-296?

A. Remind what that is.

Q. That is a paper by a Dr. Walters. If you didn't talk about it, then I won't ask you about it, but it was in your binder so I am just wondering?

A. I am familiar with it, but I did not talk about it.

Q. If you didn't talk about it, then I won't ask any questions about it.

THE COURT: This is a good time to break for our lunch. Okay.

MS. BROOKS: Thank you, Your Honor.

(Luncheon recess taken.)

THE COURT: Counsel, let's continue. Please be seated.

Ms. Brooks.

MS. BROOKS: Thank you, Your Honor.

BY MS. BROOKS:

Q. **Almost done, Dr. Tanna. Just a couple more points.**

We talked earlier about all the different glaucoma medications that are still on the market that have BAK as the preservative. Do you recall that?

A. **Yes, I do.**

Q. **One of the ones that I mentioned briefly was Lumigan. Are you familiar with Lumigan?**

A. **I am.**

Q. **Lumigan is of the prostamide family?**

A. **I consider it a prostamide analog. That is a subtle discrepancy between the way Allergan and some people describe it and the way as I describe it.**

Q. **For us agreeing, let's say it's part of the prostaglandin family?**

A. **I can even meet you where you are if you wish. It's semantics.**

Q. **I will meet you.**

The mechanisms of action for the prostaglandins is that the prostaglandins treat glaucoma, or lowering of intraocular pressure, by increasing the uveoscleral outflow?

A. **That's correct.**

Q. **Is that, as a physician, your preferred method of action, rather than, for example, decreasing aqueous humor**

production, you would rather increase the outflow, the uveoscleral outflow?

A. **In general, my preference would be improved outflow, if I had a choice of how a particular medication works. But it does not matter to me whether it's by uveoscleral outflow or tubular pathway outflow, because outflow medications are better than medications that reduce aqueous production, in my opinion. There is no evidence of that, by the way.**

Q. **In your opinion, even though there is no evidence of that, your personal opinion is you prefer those types?**

A. **Yes.**

Q. **The ones that increase the outflow rather than decrease the production?**

A. **Correct.**

Q. **One of those is this Lumigan drug we talked about. Correct?**

A. **Correct.**

Q. **The active ingredient in Lumigan is called bimatoprost?**

A. **Correct.**

Q. **Allergan manufactured that. Correct?**

A. **Correct.**

Q. **Lumigan came on the market at about the same time that Alphagan P did, didn't it?**

A. **I believe so. Within a year, I'd say.**

Q. **Lumigan has BAK as its preservative?**

A. **Correct.**

Q. **And, yet, at that point in time, when Allergan was formulating Lumigan, we know that Refresh Tears with Purite was already on the market, 1997. Correct?**

A. **Correct.**

Q. **Yet, despite that, the formulators at Allergan did not, for whatever reason, substitute the BAK in Lumigan for Purite?**

A. **That's correct.**

Q. **Now, let's go look briefly at the Katz paper that you talked about, DTX-170.**

Specifically, if we could go to Table 2, which appears on page 124, I believe that is the table you were questioned about by counsel.

While we are looking for that, let's just, I want to make sure to establish what we are looking at here. The Katz paper is talking about a study that was done internally at Allergan, I believe you told us. Is that right?

A. **No. This study was a multi-central clinical trial. It was done at numerous centers.**

Q. **That's right. I am sorry. But it was sponsored by Allergan?**

A. **This is the one, it's the two FDA pivotal trials, 007**

and 008. Those are the Allergan internal document references to those two clinical trials.

Q. **And those two pivotal clinical trials turned into what was FDA approval for Alphagan P?**

A. **That was part of the NDA.**

Q. **Now, if we look at what this particular -- the various formulations that are being tested here, the first column is brimonidine Purite .15 percent. Is that right?**

A. **That's correct.**

Q. **Then our next formulation is brimonidine-Purite .2 percent. Is that right?**

A. **That's correct.**

Q. **Then the next formulation is brimonidine .2 percent?**

A. **Correct. The original formulation.**

Q. **All right. So the very third column is the original formulation. That's Alphagan. Is that right?**

A. **Yes.**

Q. **Now, if one wanted to see whether or not it was the BAK, the preservative, that was in Alphagan that might be causing, for example, the allergic conjunctivitis, one way to do that would be to substitute the BAK for the Purite. Correct?**

A. **Correct.**

Q. **But if you did that, you would want to make sure that you kept everything else the same in order to be able to**

really focus in on whether it was the BAK versus the Purite. Right?

A. **That's correct, yes.**

Q. **So if you look at formula 2, the amount of brimonidine in that formula is the same as the amount of brimonidine in the original Alphagan. Correct?**

A. **Correct.**

Q. **Then formula one, we have got not only the change of the BAK, the Purite with the BAK, but we have a lowering of the amount of active ingredient, the brimonidine?**

A. **Correct.**

Q. **Now, if we could compare the number in allergic conjunctivitis between Alphagan P, which would be the first column, and brimonidine .2 percent with the Purite, which would be the second column, and then the original Alphagan, what is it we see here, Dr. Tanna?**

A. **What we see -- we see three numbers that give us an idea of the incidence of allergic conjunctivitis, that particular adverse event, in the three formulations, with the three formulations.**

Q. **What we see is that, with formulation No. 1, what would turn into Alphagan P, we see an incidence of 9.2 percent?**

A. **Correct.**

Q. **And brimonidine-Purite .2 percent, we see an incidence**

of allergic conjunctivitis of 14.6 percent?

A. **Correct.**

Q. **And then with the original Alphagan, we see an incidence of allergic conjunctivitis of 15.7 percent?**

A. **That's correct.**

Q. **Thank you.**

Would you agree that as a physician, or physicians as a whole, especially those that have specialties, that you are sophisticated consumers when it comes to what drugs you are going to prescribe to your patients?

A. **Not exactly. I mean, I like to think that I am, that I critically review the literature. But I don't think everybody responds to the literature the same way. I think that a lot of clinicians rely on marketing materials to make clinical decisions, unfortunately, when it comes to pharmaceuticals.**

Q. **Specialists like you, for example, Dr. Tanna?**

A. **Well, when you say like me, do you mean somewhat in an academic institution?**

Q. **How about BAK, somewhat in an academic medical institution would tend to look beyond simple flashy marketing material?**

A. **Correct, I think, for the most part, that is true.**

Q. **And certainly someone, for example, who has a**

subspeciality in ophthalmology, that subspeciality being glaucoma, would want to focus in on the glaucoma medications that are being offered for treatment?

THE COURT: What do you mean? I don't understand.

MS. BROOKS: I apologize, Your Honor, that was really vague.

BY MS. BROOKS:

Q. **Dr. Tanna, as a specialist in the subspecialty field of glaucoma, would one want to look deeper than just marketing material to determine whether or not you would want to prescribe a particular drug?**

A. **I think I can safely speak for myself. I can say that, as an academic ophthalmologist responsible for teaching residents and medical students, that I don't rely on marketing materials. In fact, I try not to look at marketing materials, to the extent possible, in order to make my decisions in order to understand what's out there and what the product characteristics are.**

I like to rely on peer-reviewed literature.

Q. **Now, you originally prescribed Alphagan, did you not?**

A. **I did.**

Q. **And then I believe you told us on direct examination that, at some point, Allergan withdrew Alphagan from the market. Is that correct?**

A. **That is correct.**
Q. **And then, for those patients whom you wished to keep on brimonidine, you began prescribing Alphagan P?**
A. **Because there was no choice. Correct.**
Q. **When you say "because there was no choice," there was certainly still Alphagan available at the pharmacies for a period of time after Allergan withdrew Alphagan from the market. Correct?**
MR. SODIKOFF: Objection. Calls for speculation.
THE COURT: Overruled.
BY MS. BROOKS:
Q. **If you know, sir.**
A. **My recollection is it was not very long at all. I don't think there were huge supplies that were available that were being exhausted. There were supplies available in pharmacies. But I think they shriveled away pretty quickly.**
Q. **And then, for a period of time, Allergan withdrew Alphagan from the market in August of 2002. Is that correct?**
A. **I don't recall the month.**
Q. **Would you accept that in June of 2003, less than one year later, generic versions of the original Alphagan were released onto the market?**
A. **I can't verify that in any way, based on my**

recollection of when the generic became available. I would have guessed, had you asked me, that it would have been later than that. But I haven't studied that particular issue and I don't really know the exact date.

Q. **Would you accept that it might be June of 2003 when the generic of, the original Alphagan came onto the market?**

A. **I don't know that. My thought is the generic brimonidine has not been around that long. So I can't really accept that.**

Q. **You have no way to know one way or another?**

A. **Correct. Because, again, like I said, my sense is it was more recent than that.**

Q. **And certainly once generic, whenever it was, once the generic brimonidine, .2 percent, came onto the market, you, as a physician, were perfectly free to prescribe it. Correct?**

A. **Absolutely, yes.**

Q. **But, in fact, even after the generic Alphagan came on the market in, let's accept for the moment June of 2003, a substantial amount of your prescriptions remained Alphagan P, did they not?**

A. **That's correct.**

Q. **And that has continued to this day?**

A. **A substantial amount of my prescriptions for brimonidine remain Alphagan P.**

Q. **As a physician, I assume that, especially a very educated physician, as you are, you would want to make sure that you were prescribing something versus the generic, and branded, because it gave either a better efficacy profile or a better safety profile?**

A. **There should be an advantage.**

MR. SODIKOFF: Objection. Compound.

THE COURT: It is compound. The problem is not whether he will understand the question but whether I can understand the answer to the compound question.

MS. BROOKS: Let me break it down.

It was done in the disjunctive.

THE COURT: It was, now that you mentioned it.

MS. BROOKS: I am trying to ask either one.

THE COURT: Why don't you rephrase. I got you.

BY MS. BROOKS:

Q. **As an educated physician, Dr. Tanna, you would want to see either a better efficacy profile or a better safety profile for the branded drug if you were going to continue to prescribe that over the generic?**

A. **Yes. I agree with that.**

MS. BROOKS: Thank you. No further questions.

THE COURT: Okay. Redirect.

MR. SODIKOFF: Thank you, Your Honor.

Your Honor, first off, I would like to apologize

on behalf of our group for coming in a little late there.

THE COURT: As you noticed, I didn't wait. It's in your interests to be in the seats when I tell you.

MR. SODIKOFF: I agree.

REDIRECT EXAMINATION

BY MR. SODIKOFF:

Q. Dr. Tanna, a lot of the cross focused on one of skill in the art according to Dr. Banker's definition. I would just like to look at that again, to make sure we are clear here about whether you're one of skill in the art, and if you are not, whether you are pretty close.

If we could put up PTX-602, please. If we can go to Page 7 of this.

Dr. Tanna, what was your undergraduate degree in?

A. Biology.

Q. Did you take courses in chemistry and organic chemistry and similar science-related courses?

A. I did.

Q. Did you take courses in science during med school?

A. Well, medical school is a series of courses that also cover basic science.

Q. Are there some that are related to chemistry during med school?

A. There is biochemistry, which I had placed out of, in

fact.

Q. What does it mean that you "placed out of"?

THE COURT: Took a test.

MR. SODIKOFF: Thank you, Your Honor.

BY MR. SODIKOFF:

Q. I would like to look at the last sentence here, "If the worker's formal education is not in the pharmaceutical sciences or pharmacology, per se" -- that might be you. Correct? I am sorry.

Are you in a related field, such as chemistry? Was your formal -- would you consider your formal education to be in a field that is related to chemistry.

THE COURT: Could I see counsel for a moment? I may be able to help you along.

(The following took place at sidebar.)

THE COURT: If you are making an effort to qualify him as one of skill in the art --

MR. SODIKOFF: I am not doing that.

THE COURT: You are really swimming upstream on that issue. And I can tell you right now that he has accepted it, by his own testimony. And I will so rule that he is not one skilled in the art.

(End of sidebar conference.)

BY MR. SODIKOFF:

Q. Dr. Tanna, prior to 1999, did you have years of

experience in using glaucoma medications?

A. **Yes, I did.**

Q. **And although you don't consider yourself one of skill in the art, do you interact with those of skill in the art as part of your practice?**

A. **As part of my practice? I wouldn't say as part of my practice.**

Q. **Have you consulted for brand drug manufacturers who are formulating products?**

A. **Yes. But in the process, I don't directly interact with people I would consider of skill in the art. Not directly. It's through intermediaries.**

Q. **Do you feel comfortable testifying about what you would like to see in a medication on the results side?**

A. **Yes, very comfortable.**

Q. **And have you expressed any of those concerns in the past with people from a pharmaceutical company?**

A. **I have.**

Q. **Do you feel comfortable basically understanding what one of skill in the art would look for, at least as to the clinical or the therapeutic effectiveness of a drug?**

A. **I do.**

Q. **Now, if we can look at, I believe it was JTX-044. At the top, if we can highlight under the first recommendation. Dr. Tanna, you have been here for the testimony of, for most**

of the testimony, I think, of everyone besides the first half of Dr. Whitcup. Is that correct?

A. That's correct.

Q. Have you seen counsel from Allergan show any of their formulators a publicly available document that showed that there was a concern regarding the stability of brimonidine and the possibility that it would oxidize?

A. "Publicly available" meaning something that would be available to somebody outside the company?

Q. Yes.

A. No, I haven't.

Q. Have you reviewed any literature regarding the oxidative stability of brimonidine tartrate?

A. I have seen two papers that have dealt with that issue.

MR. SODIKOFF: Your Honor, I would like to go to DTX-296, which I think is actually in your booklet, although we didn't mention it earlier.

BY MR. SODIKOFF:

Q. Dr. Tanna, can you tell me the title of this article?

A. "Development and Use of Brimonidine in Treating Acute and Chronic Elevations of Intraocular Pressure: A Review of Safety, Efficacy, Dose Response, and Dosing Studies."

Q. When was this article published?

A. It was published in November 1996.

Q. **I would like to look at the second page of this document, S20 on the top left, the first paragraph on the top left, can you read where it starts with "Brimonidine"?**

A. **"Brimonidine is a highly selectively alpha-2-agonist, 28 times more selective than Apraclonidine and ten times more selective than Clonidine."**

Q. **What does the next sentence say?**

A. **"Ocular allergy occurs less than with Apraclonidine, which may be related to its oxidative stability."**

Q. **Does this tell you anything about the oxidative stability of brimonidine?**

A. **It suggests that brimonidine is at least more oxidative, more stable in terms of oxidative injury than Apraclonidine.**

Q. **Dr. Tanna, earlier in your testimony, if we can go back to the Derick article, I think it's DTX-111, and if we can go to the table, I am sorry, I don't have it with me, that counsel was referring to, counsel for Allergan, the next page, Table 3, I believe during the cross, you wanted to say something and counsel said you could do it on our time, regarding Table 3 and what you look for, what types of testing that you look for in determining efficacy. You are now on our time.**

Can you explain what you wanted to say?

A. **What I wanted to say is that I have personally dealt**

with putting together a table or two like this in a paper.

I know that there is a drawback to doing this, that is, that you can sort of pick any percent threshold that you want and keep trying things until something works, which is why, when we did it, we weren't looking at the data, and my co-author and I decided ahead of time what threshold we were going to use. And it was only one number, if I remember correctly.

So analyses like this one, to me, are suspect. This is not the way I like to judge efficacy of a drug. I like to see the mean, either percent reduction in IOP or the mean antiocular pressures and standard deviations. And, here, we just don't have the robust quality of data to make meaningful conclusions.

Q. **If we can look at this entire page. Just look at the chart on the top right.**

I would actually like to go back to DTX-296 as a side, dual column.

I will just go into this because I think it's a better picture of the graph. I think we will see it's the same one.

Q. **It's Page S 23 at the top. If you could blow that graph up?**

Dr. Tanna, do these look like -- would you agree with me that this is the same data being presented in these

different articles but similar graphs?
A. It's the same data, but the abscissa is different in terms of the range presented. So the graph looks different, but it's the same data. I know that from having read both papers.
Q. Actually, in DTX-296, if we go to the previous page, S 22, under "Dose Response Study," where there is a footnote 10, Footnote 10 there, if we go to the references pages, S 25, Footnote 10, that is the Derick article we have been talking about. Correct?
A. Correct.
Q. If we can go and just look at the chart in this Walters article, DTX-296, at S 23, at the top, and just blow that one up alone?
Dr. Tanna, can you mark where the .08 is on there? Can you just identify it?
A. Yes. .08 is this line (indicating.)
Q. And the .2 percent?
A. .2 is this line (indicating). They extend up here as well, but it is harder to distinguish them.
Q. If you can erase those.
A. (Witness complies.) Do you want me to make them all go away and start over?
Q. Yes. Do you see a significant difference in efficacy between the .08 and the, I don't want to say significant,

but how would you qualify the difference in the efficacy between the brimonidine .08 percent and the brimonidine .2 percent?

A. **They are similar.**

Q. **And, overall, are the two lines converging as we go further along in time or do they seem to be separating?**

A. **Well, they seem to be converging. But I don't think that we can really extrapolate beyond this time duration. I don't think that that would be reasonable.**

Q. **You would want to see a clinical study to actually extend this time period for three months or a year?**

A. **Right. I think what we can say is that the paper tells us that there is no statistically significant difference between those two, because it does report a statistically significant difference between the .08 and the .5, I believe. But there is no statistically significant difference in this graph with the data that are represented in this graph between the .08 and the .2.**

Q. **If we can move to JTX-003, Figure 1. Can you mark on here where .08 percent brimonidine tartrate would be, along the y axis.**

A. **(Witness complies.)**

Q. **Now, counsel, during the cross-examination, was suggesting that therapeutically effective concentrations of brimonidine tartrate would not be soluble at a pH that is**

similar to the pH of the eye.

The pH of the eye is what?

A. **The relevant pH of the tear film in the tears, that is the relevant pH, and it's 7.4.**

Q. **Here, and according to the Derick article, which said there was a therapeutic effective amount at .08, would that be soluble at 7.4, just looking at this chart?**

A. **Yes.**

Q. **I would like to just move on briefly to the marketing.**

Counsel was talking about ophthalmologists and that a subspecialty within ophthalmology is glaucoma treatment people. Is that correct?

A. **Glaucoma is a subspecialty within ophthalmology.**

Q. **Do ophthalmologists, themselves, treat some patients with glaucoma?**

A. **The vast majority of patients in the United States who have glaucoma are treated by general ophthalmologists.**

Q. **Is it fair to conclude from that that the vast majority of prescriptions are written by general ophthalmologists?**

A. **Yes, that is a fact.**

Q. **What is your opinion regarding, if you have one, regarding whether or not general ophthalmologists focus too much on marketing materials?**

A. **I read an interesting article recently that stated**

that, among the specialties, ophthalmologists are the ones most likely to use branded products and to not use generics.

I think that that is because of our susceptibility of being a specialty and because of the skill of the marketing that is directed toward us.

Q. Finally, Dr. Tanna, the original -- the generic form of the original Alphagan is not AB-rated to the Alphagan P .15 percent. Is that correct?

A. That's correct, which, as I understand it, means that the pharmacist dispensing the product cannot substitute Alphagan P as equivalent to Alphagan original formulation.

MR. SODIKOFF: Thank you. No further questions.

THE COURT: All right, Doctor. Thank you.

(Witness excused.)

MS. BROOKS: Your Honor, Allergan will call as its next witness Joe Schultz, and Mr. Marsden will be doing the examination.

THE COURT: Just give me a second. I will be right back.

MR. BREISBLATT: Your Honor, may Dr. Tanna be excused?

THE COURT: I have excused him.

(Pause.)

THE COURT: Let's get the witness on the stand.

MR. MARSDEN: Thank you, Your Honor.

Allergan calls Joe Schultz.

JOSEPH SCHULTZ, having been duly sworn as a witness, was examined and testified as follows ...

MR. MARSDEN: Your Honor, may I approach to give Mr. Schultz his binder?

THE COURT: Yes, Mr. Marsden.

MR. MARSDEN: I have binders for the Court as well.

Your Honor, since we had a brief break in our case to accommodate Dr. Tanna, may I give a very brief transition statement?

THE COURT: Yes.

MR. MARSDEN: We are calling Mr. Schultz to shift back to the commercialization of the inventions and how the Alphagan P products have been received in the marketplace. We are specifically going to focus on what happened when Alphagan P original formulation was introduced, what happened when generics came on the market, and then what happened when Alphagan P .1 percent came on the market.

DIRECT EXAMINATION

BY MR. MARSDEN:

Q. **Good afternoon, Mr. Schultz.**

A. **Good afternoon.**

Q. **Could you introduce yourself to the Court, please?**

A. **Yes, my name is Joseph Schultz.**

Q. **Where do you work, Mr. Schultz?**

A. **I work at Allergan.**

Q. **What is your position at Allergan?**

A. **I am the senior vice president of the U.S. eye care business at Allergan.**

Q. **How long have you been at Allergan?**

A. **Approximately five years.**

Q. **What did you do before that?**

A. **I worked in the pharmaceutical industry about for 20 years, the previous 13 years at Johnson & Johnson.**

Q. **Could you briefly describe your educational background for the Court?**

A. **Yes. I have an undergraduate degree in biology from Elizabethtown College in Pennsylvania and a Master's in business administration from Fordham University in Manhattan.**

Q. **What are your responsibilities as the senior vice president of U.S. eye care for Allergan?**

A. **I am responsible for oversight of the commercial operations for the U.S. eye care business. I have sales and marketing reporting into me.**

Q. **How many products does Allergan sell in your business?**

A. **Allergan has a very broad portfolio of ophthalmic**

products. We have been in the ophthalmic business for over 60 years. So we have a large heritage of products.

But, most recently, we support usually eight to ten products of our newer products in the portfolio.

Q. Do you have an understanding of what products are at issue in this case?

A. I do.

Q. What is your understanding?

A. Alphagan and Alphagan P .15 and .1.

Q. What is Alphagan?

A. Alphagan is brimonidine. It is an IOP lowering drug for glaucoma patients.

Q. Is Alphagan still offered in the marketplace by Allergan?

A. Alphagan .2 percent is not.

Q. Were there any problems with Alphagan?

A. When you look back at the history, Alphagan was a relatively successful product in the market. But from --

MR. SODIKOFF: Your Honor, objection. This witness didn't join Allergan in 2004 and is testifying to facts about which he has no personal experience.

MR. MARSDEN: Your Honor, I can lay a foundation, if you would like.

BY MR. MARSDEN:

Q. When you joined the company, did you become familiar

with its product line and the history of that product line?
A. I did.
Q. In the course of that, did you learn whether there had been any problems with the Alphagan product when it was on the market?
A. Yes.
MR. SODIKOFF: Objection. Again, this is a fact witness, not an expert witness. He has no personal experience with what happened prior to his joining the company.
THE COURT: If the experience is based upon admissible evidence, would you agree, such as business records?
MR. SODIKOFF: If the witness identifies the information he is relying on.
THE COURT: Could you have him do that, Mr. Marsden.
MR. MARSDEN: Certainly, Your Honor.
BY MR. MARSDEN:
Q. Mr. Schultz, when you joined the company, how did you familiarize yourself with the Allergan product line?
A. Honestly, it is the responsibility of me to learn the products, the portfolio, so a number of ways. Obviously, looking back at some of the research around the products, also, speaking to the clinicians who have used our products

over the years, which I do on an ongoing basis today as well. Even as of today, clinicians will talk about some of the challenges they had with the original Alphagan.

Q. What were some of those challenges?

A. The main challenge that they faced --

MR. SODIKOFF: Objection, Your Honor.

(The following took place at sidebar.)

THE COURT: You heard the objection.

MR. MARSDEN: Yes.

THE COURT: What is your response?

MR. MARSDEN: We anticipated the objection, Your Honor. This is an exception to the hearsay rule. The state of mind of the customers and their motivation towards changing to the new drug.

THE COURT: Overruled.

(End of sidebar conference.)

BY MR. MARSDEN:

Q. I will pose a new question, Mr. Schultz, so we don't lose time reading it back.

What were the problems with Alphagan that you learned from your investigation into the products of Allergan?

A. The main concern the physicians usually voiced in the research and also -- was the tolerability profile of the product, particularly as it related to ocular allergy as

well as some of the other smaller, more nuisance side effects.

Q. What is Alphagan P?

A. Alphagan P is a newer formulation of brimonidine that included either a .15 or a .1 percent of concentration of drug. And that product provided not only the same -- both products provided not only the same level of efficacy of the original .2 percent but improved the tolerability profile.

Q. When was Alphagan .15 percent first introduced?

A. That would have been in August 2001.

Q. When was Alphagan .1 percent introduced?

A. That would have been February 2006.

Q. In your experience, in your job at Allergan, has Alphagan P been a successful drug?

A. Yes. It's a very successful product, not only from the company's perspective, but within the branded glaucoma market, it is one of the most successful products in the market.

Q. What were the sales of Alphagan P last year?

A. Approximately $240 million.

Q. Now, other than the sales dollars, how else do you quantify the success of a drug at Allergan?

A. We look at a number of metrics. We look at prescription trends, both total prescriptions as well as new prescription trends over time. We look at those relative to

competitors' prescription trends as it relates to market share of prescriptions.

Q. Now, in your role as the senior vice president of U.S. eye care, do you subscribe to and receive market data regarding prescription rates?

A. Yes, we do, on both a weekly and monthly basis.

Q. Let me ask you to turn to PTX-249, which should be in the binder that is in front of you.

A. Yes.

Q. We have it up on the screen as well. It's a little hard to read.

Can you describe generally what we are looking at?

A. Yes. This would be a typical report of ongoing prescription trends. This one happens to be for the total glaucoma market. It is for total prescriptions, or TRx's, and it outlines not only what the total market trends were on a month-by-month basis from, it appears, November 1993 through 2000 -- early 2006. Then it also shows those same trends by some of the major categories and some of the major products within those categories.

Q. And we know this is the total glaucoma market because we can see that up in the upper left-hand corner. Is that correct?

A. That is correct. So, for the month of November, 1993,

the total glaucoma market was about 1.2 million prescriptions for that month.

Q. **We can see that by reading along the rows. Is that right?**

A. **That's correct. And as you move to the right, it gives each additional month worth of data.**

Q. **Total market appears at Row 8?**

A. **The total market does appear at Row 8, that's correct.**

Q. **Before we leave this first page, what is TRx, TR small X?**

A. **TRx stands for total prescription trends. That would include new prescriptions or new pieces of paper that a physician pens a new prescription, either because the patient is new or the refills have run out and they have to write a new prescription. It includes both the refills as well as any new prescriptions.**

Q. **Do you sometimes also receive market data just on new prescriptions?**

A. **We do.**

Q. **We will come back to that in a moment. If we can stay on Page 1 for a moment. Does this report also report prescriptions for Alphagan?**

A. **Yes, it does. Alphagan would appear, it appears to be Line 21.**

Q. **Does it report sales of Alphagan P?**

A. **Yes. That would be on Line 22.**

Q. **Does it report sales of generic brimonidine?**

A. **It does, on Line 23.**

Q. **Staying on this first page just a little bit longer, where did these figures come from?**

A. **These figures, the sources on the document are from Verispan, which is one of the several third-party independent audits that are available to industry or to anyone who is going to purchase them.**

Q. **Mr. Exline, if we could back out and show that at the bottom of the page, in the lower left-hand corner.**

Is that what you are referring to?

A. **That's correct. Verispan is the name of the company and VONA is the actual name of the audit itself.**

Q. **Is that data available to other companies in the industry as well?**

A. **It is.**

Q. **Can you remind us, again, what was the launch date of Alphagan P?**

A. **Alphagan P was launched in August 2001.**

Q. **Can you turn in Exhibit PTX-249 to August, 2001, and show us where we see the first sales of Alphagan P?**

A. **That would appear to be on Page 11. You can see if you follow across Line 22, the first prescriptions are marked in August of 119 prescriptions.**

Q. **And before we follow what happened when Alphagan P came on the market, what was the total market for glaucoma prescriptions in August of 2001?**

A. **It was approximately 1.8 million prescriptions per month.**

Q. **Where do you get that number from?**

A. **The very top, it would be Row 8.**

Q. **And if you look to the very end of this chart, what was the total market in April of 2006?**

A. **Approximately 1.8 million prescriptions as well.**

Q. **So there wasn't much change in the total market, then, during that period?**

A. **No, it is a relatively slow changing and slow growth market.**

Q. **Now, what did you observe in the marketplace when Alphagan P came on the market?**

A. **Well, what you can see, if you look at Row 22, as it moves across, that, relatively quickly, Alphagan P prescriptions grew month over month. At the same time, that was very much at the expense of Alphagan, which was declining at the same time.**

Q. **So, is it correct that Alphagan and Alphagan P were both on the market for a period of time after Alphagan P was launched?**

A. **That's correct, for approximately a year.**

Q. **And when did Alphagan cease selling Alphagan?**

A. **That would have been August 2002.**

Q. **So, for the period of roughly August, 2001, to August, 2002, Allergan was selling both Alphagan and Alphagan P.**

A. **That's correct.**

Q. **Have you prepared a demonstrative to show what happened to the relative prescription rates of the two drugs during that period?**

A. **Yes, there is a demonstrative.**

Q. **Could we pull up ADX-16, please.**

What does this show, Mr. Schultz?

A. **This graphically depicts, on a monthly basis, the data that is included in this report. And you can see the launch of Alphagan P at the beginning of the chart, obviously it started at zero prescriptions, and as it increased very, very rapidly, that was very much at the expense of Alphagan .2 percent. And by the time we got out to that the July-August time frame, the prescriptions for TRx's were approximately split 050-50.**

Q. **Where did the data come from that you used to make up this chart?**

A. **This data, once again, is Verispan data and it's the same data that is included in the report that we discussed.**

Q. **Do you have an understanding of why you saw this phenomenon in the marketplace when Alphagan P came on the**

market?

A. It was very clear --

MR. SODIKOFF: Objection. Foundation.

THE COURT: Overruled.

THE WITNESS: It was very clear, from the research that, as we have already discussed, the biggest issue physicians had with base Alphagan was that it had a relatively high allergy rate. And Alphagan P had the promise of a lower allergy rate due to the lower concentration, but, at the same time, provided the same clinical effect, the same level of efficacy.

So what it was to the physicians was a solution to the challenge they faced with Alphagan, they very quickly adopted it, got experience with it, found a very good response, and continued to prescribe Alphagan P over Alphagan.

Q. Now, I think you testified earlier that PTX-249, from which this graph was created, was total prescriptions. Correct?

A. That's correct.

Q. But you do sometimes also look at new prescriptions?

A. We do. They often are a leading indicator of what is happening, because as physicians are writing new prescriptions, it is weeding out those TRx's which are just being refilled and it shows actually what physicians are

doing as they are writing out a paper for the patient to pick up a new prescription.

Q. **If you could turn in your book to JTX-90. What is JTX-90?**

A. **This is new prescription data that looks at a three-month period of time, May 2002 to July 2002. Specifically looking at just the new prescriptions for Alphagan P versus Alphagan or base Alphagan. What it shows is how rapidly physicians were changing their prescribing to Alphagan P despite the fact that base Alphagan was still available.**

So, from the month of May, 2002, it was already 43 percent. Within two months, it jumped to over 55 percent. Once again, a leading indicator for physicians' preference of Alphagan P.

Q. **What was the source of data in this chart?**

A. **This is, once again, a Verispan audit. It is not the VONA database or the Scott Levy (phonetic) database. But Verispan Company has several databases that track that type of information.**

Q. **We have seen the increase in the market share of Alphagan P when it came in the market during the time when Alphagan was still in the marketplace.**

Did Allergan have a marketing launch when Alphagan P came on the market?

A. **Yes, of course we did, to educate physicians around this new product. Obviously, from an education and a commercial perspective, knowing that their history and their concerns with Alphagan were the allergy, the fact that we could provide a new product that significantly reviewed that adverse event, but, at the same time, provided the same level of efficacy that they were confident in and appreciated, was an opportunity to, No. 1, reengage some clinicians who may not have used the product or had used it and had bad experiences with allergy, and also to reengage physicians who had been using the product and show them that this product could have significant utility in their products that they have available to treat glaucoma.**

Q. **Well, isn't this increase in sales just a reflection of the marketing campaign that you have?**

A. **I don't think it's just the level of communication and marketing. We deal with a very, you know, educated customer base. These individuals, very often, are skeptical of new products, are skeptical of just marketing messages, and often want to evaluate a product and use it for themselves. So if the product didn't deliver on the promise, our customers would not have had a lot of reason to feel that they saw the benefit of Alphagan P and switch patients to Alphagan P.**

Q. **Now, in addition to tracking this prescription data in**

the regular course of your duties at Allergan, do you conduct market research?

A. **We do, on an ongoing basis.**

Q. **Was market research conducted at the time Alphagan P was launched?**

A. **Yes, it was.**

Q. **And are you familiar with that research?**

A. **I am.**

Q. **What did that research show?**

A. **There were a number of things that were being looked at, trying to really assess physicians' knowledge and attitudes of Alphagan versus Alphagan P, what their experience was and what their thoughts were around the product.**

Specifically, what came back is that, as we had already known, physicians' concerns with base Alphagan was the level of allergy and adverse events, that their experience with Alphagan P was very, very positive, and their feedback was that they really didn't need both products. That only Alphagan P was their main preferred product and they felt needed to be available.

Q. **So what did Allergan do?**

A. **Allergan, with that information, decided to remove Alphagan from the market, stop the sales and marketing of the product and put all our energies and efforts into**

Alphagan P.

Q. **And that was August of 2002?**

A. **That was in August of 2002.**

Q. **Now, when Allergan stopped selling Alphagan in August of 2002, were any generic Alphagan products on the market?**

A. **They were not.**

Q. **When were the first .2 percent generic brimonidine products sold in the marketplace?**

A. **I believe it was June of 2003.**

Q. **If you can return to PTX-249 that we looked at earlier. Can you look at June 2003 to see if it confirms that there were sales of generic brimonidine as of that date?**

A. **Yes. You can see on Line 23 the first noted prescription for generic .2 percent brimonidine.**

Q. **But there was a period of time, you would agree, from August of 2002 until June 2003 when Alphagan P was the only brimonidine drug available on the marketplace?**

THE COURT: Mr. Marsden, is that August '01 or August '02?

MR. MARSDEN: August '02 is when the Alphagan product was no longer sold by Allergan.

THE WITNESS: So, yes. Between August '02 and this time frame, there was not a brimonidine .2 percent product available on the market, that's correct.

BY MR. MARSDEN:

Q. **Didn't that mean that doctors were forced to convert their patients from Alphagan to Alphagan P during that period?**

A. **No. Doctors were not forced to convert. Doctors needed to make a decision on what they wanted to prescribe for their patients.**

The timing would have required any patient who went to fill a prescription for Alphagan a re-consult with the physician, whether it be a phone call from the pharmacy or discussion with the physician to make a decision what they wanted to prescribe.

During that period of time, there, obviously, were a whole slew of glaucoma medications that they could choose from. The prostaglandin analogs were very heavily being discussed at that point, since two were just launched earlier that year. There were a number of other products, obviously, Alphagan P was available, Cosopt, Trusopt, and Azopt, generic timolol, branded timolols. So the whole potential portfolio of products were available to physicians when they were needing to make a change for those patients from the product they were on, Alphagan was no longer available.

Q. **Now I want to shift your focus to the second area that I told the Judge we would talk about, which is what happened**

when the generic Alphagan products came on the market in June 2003.

What did you observe in the marketplace at that time?

A. **Well, as the generics came onto the market, you can see, actually, if you track across the prescription data, there was kind of a slow, somewhat steady uptake of the generic. And then, after a period of time, the generic flattened out and did not make anymore progress in its gains in market share or prescriptions.**

Q. **You can see that in the data that we started looking at, at Page 13 of PTX-249. Is that correct?**

A. **That's correct. If you follow it month by month across in that Line 23, you can see that it gradually gets gains and then levels out somewhere around the, say, 25,000 prescriptions per month by the time this data is complete in 2006.**

Q. **Have you prepared a demonstrative exhibit to show the change in prescriptions of Alphagan P when generic .2 percent brimonidine was introduced?**

A. **Yes. There was a graphic depiction of the data.**

Q. **Could we pull up ADX-8, please.**

Is this that demonstrative?

A. **That is. Once again, you can see from the launch of the generic on the red line, or the generics, I should say,**

because there were several, that it had a relatively slow uptake, flattened out, and the general trend was toward the ten to 15 percent range, about 12 percent, the most recent data that I looked at. And you can see that it had a relatively minor impact on the -- on branded Alphagan P.

Q. **Once again, where did the figures come from that were used to draw this demonstrative?**

A. **This data is, once again, from the same data source we just looked at, the Verispan, VONA audit.**

Q. **Just so we are clear, that data picks up starting in June of 2003 on the left-hand side. Correct?**

A. **That's correct.**

Q. **And that is when the generic brimonidine products first came on the market?**

A. **That's when they first came to the market, that's correct.**

Q. **Now, during your experience at Allergan, have you seen generics come onto the market?**

A. **Yes.**

Q. **Is this what you normally see when a generic comes onto the market?**

A. **No. Very often, generics can cannibalize a brand very, very quickly, within several months. If you look at some of the historical models, 70, 80 percent. The most recent product, Cosopt, was taken over by the generic within**

about 70 to 80 percent, within five to six weeks.

Q. Just so we are clear here, does the Alphagan P that is shown here include both the .15 and the .1 concentrations?

A. It does. It's the entire Alphagan P family. Alphagan P, though, launched just at the very end of that chart in February '06. So only the very end of that chart would include the Alphagan P .1 percent.

Q. Do you have any understanding from your work at Allergan as to why the Alphagan P product was not taken over by the generic here?

A. Well, it was very clear, from all the research that we did at the time and what we have done now, is that physicians saw extreme benefits of Alphagan P over base Alphagan. So they saw the same level of efficacy that they expected and enjoyed with the .2 percent, but they saw an improved tolerability profile.

So the value of the product, in physicians' minds, was significantly higher, and by going to the generic .2 percent, that was like going backwards. So most physicians looked forward in using newer, more advanced technologies, which is not going backwards. And this is, in fact, a backwards step for many of their patients.

Q. Today, how many generic brimonidine products are there on the marketplace?

A. There are approximately five or six.

Q. **When these companies came on the market with their generic brimonidine, did they have marketing campaigns.**

A. **Yes. In particular, Bausch & Lomb, and Alcon, with their Falcon brand, promoted and had marketing efforts, again, pharmacies, samples in physicians' offices, et cetera.**

Q. **If we just look at the top line, Alphagan P, it actually looks like it is declining slightly over time. Is that correct?**

A. **That's correct.**

Q. **How do you account for that?**

A. **Some of the impact is from by the share that the generic did take. Although small, obviously, it did take it from some of the brimonidine business. Also, this chart really only depicts a very simple single dynamic going on in the market at the time, it is the generic brimonidine versus Alphagan. But there are many other things going on in the market.**

As I mentioned earlier, just earlier in the same year, 2003, two prostaglandin analogs were launched, one by Alcon and one by Allergan. And prostaglandin analogs had, to some extent, become the standard of care or the first line therapy of choice. So they were having a big impact on the market in general. As patients were being moved to what were a new class of more effective drugs which were more

convenient, with once daily dosing, were more potent in lowering IOP, and, in some cases, could move patients from a multiple drug to a single drug.

So all the dynamics are going on in the background here. And despite all those specific dynamics, Alphagan P did very, very well commercially in the market and continues today to maintain its position as the number one adjunctive therapy available in the market today, it is a branded product.

Q. **You said "adjunctive therapy." What did you mean by that?**

A. **As I mentioned, the prostaglandin analogs have kind of become the standard of care. So they are usually the first line therapy. It is what most patients are put on in their initial therapy. When the physician is not getting the effect they need, they are not getting enough pressure lowering the effect with one drug, they will add a second drug, and that second or third drug they add is called an adjunctive drug.**

Q. **What is Alphagan P's role in the adjunctive market?**

A. **Alphagan P is primarily used as an adjunctive. And it is the leading branded adjunctive in the market today.**

Q. **This chart we have up here only goes to April of 2006. Do you have any more recent data?**

A. **Yes. We have data on an ongoing basis. And there is**

more recent data in some of the exhibits.

Q. If we can look at PTX-617. If we first look just at the cover of this, please.

What are we looking at here?

A. This is glaucoma, once again, prescription data. This happens to be weekly versus the previous data we looked at, which is monthly. As I mentioned, we get data both weekly and monthly. This is for the glaucoma market. Once again, it is from Verispan, one of Verispan's other audits that tracks the prescriptions on a weekly basis.

Q. If you turn to the second page, what period of time is covered by this particular report?

A. This report looks like it's from October 2007 through November 9th, 2007, on a weekly basis.

Q. What does this report show with respect to the share of the market that Alphagan P and the generic brimonidine products were obtaining?

A. Well, whether you look at the NRx data, or the new prescription data, or the TRx data, and I will refer to the NRx data on the left up there, you can see that even back into November of 2007, from the new prescriptions, Alphagan P was generating about 17,000 new prescriptions a week versus the generic, only about 2400.

Obviously, the ratio there is somewhere in that ten to 15 percent, the generic has gotten an Alphagan P

maintaining the lion's share, about 85 to 90 percent of the prescriptions on a weekly basis.

Q. **So we are clear, can you highlight the line where it says "Alphagan P." Then also the line where it says "generic brimonidine, .2 percent."**

A. **(Witness complies.)**

Q. **Once again, Mr. Schultz, what does that show?**

A. **It shows that even out here at November, 2007, that Alphagan P continued to maintain dominant share versus the generic brimonidine, about 85 to 90 percent of the NRx's, and the same trend was true of the TRx's.**

Q. **If we could just turn to the next page to confirm that. Is this the TRx's?**

A. **Yes. That is the TRx trend, and you can see November 9, 2007, once again, that the majority, 47,000, continued to remain with Alphagan P. Despite the availability of the generics, multiple generics, they had gained only about 6,000. You can see, from week to week there, they are relatively flat in that six to 7,000 range.**

Q. **Have you seen any significant change in this since the time of these reports?**

A. **No. The most recent data I have looked at is the same trend. It was about 12-and-a-half percent share in the most recent data that I looked at.**

Q. **Let's turn to the third topic that I told Judge Sleet**

we would address, that is, what happened when the Alphagan P .1 percent product came on the market?

Once again, when was that product launched?

A. That product launched in February 2006.

Q. How have prescriptions for Alphagan P .15 percent been affected by the launch of Alphagan P .1 percent?

A. In the trend, that was very similar to what happened to the .2 percent when the .15 was launched. So, over time, there has been a steady and relatively rapid increase in the .1 percent NRx's and TRx's, much of that at the expense of the .15.

Q. And is there a graph in PTX-617 that we have been looking at that shows that trend? If I could direct you to Page 6.

A. Yes, there is. As you can see on this graphic, since the launch in February of 2006 of Alphagan P .1, which is the lower line, you can see the steady upward growth as physicians have now shown their preference for the P .1 percent at the expense of the P .15 percent.

Q. Do you have any knowledge or understanding, based on your work at Allergan, as to why physicians have switched their patients from the .15 to the .1 percent formulation?

A. Yes. What physicians have told us both in research as well as what physicians have told me in dialogue, in conversations with them, is that the ability to maintain the

clinical effect at .1 percent, which is now half of the original Alphagan that was at .2, and a further reduction to the .15, is something they are very excited about. Actually, that is probably what they were most skeptical about. But the clinical data that we used to develop the product and submit it to the FDA showed equivalent efficacy of .1 and .2, and their own experience has borne that out.

But now with the .1 percent, lower than the .15 and lower than the .2, they offered the opportunity to use the lowest effective commercialized dose. Based on their experience with the .15, their feeling is that the lowest effective dose minimizes the risk of any adverse events, whether it be allergy or some of the nuisance events as well that were seen with brimonidine.

Q. **This, again, only goes through October of '07. Has the trend that is shown here continued?**

A. **That trend has continued, and, in the most recent data, the new prescriptions are about 50-50.**

Q. **Has Alphagan P .1 percent been a successful product for Allergan?**

A. **It has been.**

MR. MARSDEN: No further questions, Your Honor.

THE COURT: Thank you, Mr. Marsden.

Mr. Boggs.

MR. BOGGS: Thank you, Your Honor.

CROSS-EXAMINATION

BY MR. BOGGS:

Q. **Good afternoon, Mr. Schultz.**

A. **Good afternoon, Mr. Boggs.**

Q. **Mr. Schultz, have you read any of the patents that are involved in this lawsuit?**

A. **I have not.**

Q. **What is the marketing budget for Alphagan P .15 percent at Allergan?**

A. **Today?**

Q. **Yes.**

A. **It is approximately two to three million dollars.**

Q. **What was it last year?**

A. **Probably about three to four million dollars.**

Q. **The year before that?**

A. **I am going to say about the same.**

Q. **The marketing budget has gone down. Right?**

A. **It's -- we prioritize our investments. So all of our marketing budgets have gone down.**

Q. **Has the marketing budget for the .1 percent gone down?**

A. **We don't look at it, first one concentration then the other. The budgets are for Alphagan. The majority of all of the marketing has been on the .1 percent since the launch of the product in 2006.**

Q. **It is true, isn't it, that the commercial success of**

Alphagan P is highly responsive, highly responsive to the product's field selling efforts? Right?

A. **Most of our products have some impact from the promotional efforts. That's absolutely true. As we educate physicians, then it really relies on their personal experience to determine whether the product will be successful.**

Q. **My words were "highly responsive." The commercial success of Alphagan P is highly responsive to the product field's selling efforts. Correct?**

A. **Clearly, our representatives in front of clinicians, talking about the data, particularly when the new formulations came out, educating them on the new data, is going to garner their attention and an opportunity for us to dialogue with them about the benefits of the product, and if we are discussing a benefit that was of interest to them, that will have an impact on their interest in evaluating a product, absolutely.**

Q. **Is that a yes?**

A. **That is a yes.**

Q. **Now, I have a question for you. If we added a third line to that chart and it was generic .15 percent brimonidine, how do you think that line would look?**

A. **I think it would have responded as an interactive generic and it would have eroded the market. But as we**

know, these two are not the same product.
Q. That's right.
A. That's correct.
Q. In fact, generic .2 percent brimonidine is not substitutable for Alphagan P at the pharmacy. Right?
A. That's correct, just as Alphagan P was not substitutable for base Alphagan at the pharmacy.
Q. It's against the law?
A. Pharmacists would need a physician's directive to change the prescription, that's correct.
Q. That's right.
If there was a generic .15 percent, the pharmacist could substitute. Right?
A. Yes, that would be true.
Q. And that line would go up and this line would go down. Right?
A. Theoretically, yes, from experience and analogs in the market.
Q. What is this graph supposed to show?
A. This graph just shows that despite the entry and promotion of .2 percent brimonidine, that physicians were not willing to switch back, and, frankly, managed care plans continued to allow Alphagan P to be available on the plan because they saw differences between Alphagan P and the .2 percent brimonidine, the clinical differences, which were

lower allergy, but yet maintaining the same level of efficacy.

Q. **Do you recognize what this document is?**

A. **Yes. I saw this during the deposition.**

Q. **This is an Allergan press release. Right?**

A. **That's correct.**

Q. **This is where they are applauding the fact that .2 percent is not substitutable for Alphagan P. Correct?**

A. **I don't know if they are applauding the fact. They are stating the fact.**

Q. **And they are telling their shareholders that Alphagan P continues to have FDA marketing exclusivity. Right?**

A. **And they continue to point out that Alphagan P has some advantages over Alphagan. That's correct.**

Q. **How meaningful is this slide? Does this tell us anything real?**

A. **I think it does. I think physicians had the option at the point of any time along that curve, and even prior to that curve, to change prescriptions from Alphagan P to something else. And even in light of a generic .2 percent, managed care's ferocious movement with generics, that they did not see these products as the same product. They saw Alphagan P as a superior product with an improved tolerability profile versus .2 percent brimonidine.**

Q. **There is a well-known phenomena out there that**

physicians routinely prescribe the brand name drug. Correct?

A. **I don't know if that is a well-known phenomena. I think there are many physicians who also prescribe generics. I have not seen any data of the percent of physicians who write something in a generic form versus a brand name form.**

Q. **When you are out there talking to these doctors that you talked about during your direct examination, talking to them and getting their ideas, did you ever talk to them and ask them, Do you normally write the prescription for the brand name or do you normally write it for the generic?**

A. **I think physicians do a lot of different things. That's physician specific.**

Q. **I think so.**

When I go to the doctor, he writes my prescription, he always writes the brand?

A. **And my doctor writes the generic. There is two ends of one that are different.**

Q. **How many factors affect this chart, other than the doctor's choice?**

A. **During this period of time, there was a heavy promotion both to managed care, and managed care can swing a heavy arm and remove products, like branded products from formulary, and will push them to a very high tier, tier 3 and 4, which tends to pull out pocket from the patients.**

And that will often stimulate physicians or patients to look for alternate options. And ultimate managed care front, and, frankly, with the physician front, they saw the benefits of Alphagan P versus Alphagan, engineered brimonidine in this case.

Q. **You think, with this chart, this shows physician's choice? I think it's because the pharmacist can't substitute generic drugs.**

Are there any other factors we ought to take into account?

A. **No. I think, as you said, this demonstrates physician's acceptance and belief that Alphagan P is a better product than .2 percent brimonidine.**

Q. **Just so we are clear, I didn't say that. That's what you said?**

A. **That is correct.**

Q. **I said it's the fact that the pharmacist can't substitute?**

MR. MARSDEN: Objection, Your Honor. Mr. Boggs is not here to testify.

THE COURT: Sustained.

MR. BOGGS: I will withdraw it, Your Honor.

BY MR. BOGGS:

Q. **So, what do you spend your marketing budget on?**

A. **It depends on the product, where it is in the**

lifecycle and what are the important programs. A lot of our budgets are spent on educational programs, peer to peer programs in particular. Those are very valuable when you have an opportunity to educate physicians around something new, like, for instance, Alphagan P when it launched, from physicians who had experience with it to physicians who have not had experience with it, to share their experiences.

We also spent some on advertising, some on sampling. Those are probably some of the main areas.

Q. How much do you spend -- how much did you spend last year on free sampling?

A. I don't know that number specifically.

Q. It's in the millions. Right?

A. For Alphagan?

Q. Alphagan P.

A. No.

Q. No?

A. No. We only had about a $3 million budget.

Q. 750,000, maybe?

A. Probably less than a million.

Q. Less than a million. More than a half a million?

A. Yes, probably somewhere in that range.

Q. A half-million dollars in free samples. Do the generics do that?

A. At the time of the launch of these generics, both

Bausch & Lomb and Falcon, Alcon's generic division, had samples available to physicians.

Q. **That wasn't for a true generic of Alphagan P?**

A. **That's correct. Even though those samples were there, physicians voted with their prescription pad to prescribe Alphagan P in light of those generics being available, both as samples and in the market.**

Q. **After receiving $500,000 worth of free samples?**

A. **And I am not sure what B and L and Alcon may have provided but they could have provided the same or more.**

Q. **Now, it's true, correct, that .15 percent and 0.1 percent Alphagan P have similar side effect profiles. Right?**

A. **They have similar side effect profiles, that is correct.**

Q. **So there is really not any significant difference between those two in terms of safety. Right?**

A. **Not from the package insert statement, which is a binded package insert which brings all the data together, that is correct.**

Q. **Now, with regard to that chart that Mr. Marsden showed that showed the sales of Alphagan P .15 and Alphagan P .1 converging, what's the understood reason for that?**

A. **As I mentioned previously, physicians see the same level of efficacy that they saw with .2 and .15. But they**

feel that the lowest effective commercialized dose is the best to give the patient and has the best chance of avoiding any issues.

In most cases, with glaucoma patients, the patients are going to be on these drugs long term. And the eye care professionals are looking to avoid adverse events and concerns over time while patients are being treated.

Q. **And it's very -- I will withdraw that.**

MR. BOGGS: I have no further questions, Your Honor.

THE COURT: All right.

MR. BREISBLATT: Your Honor, Mr. Benson will be handling the cross-examination.

THE COURT: Mr. Benson.

MR. BENSON: Thank you, Your Honor. Good afternoon, Your Honor.

THE COURT: Good afternoon.

BY MR. BENSON:

Q. **Good afternoon, Mr. Schultz.**

A. **Good afternoon.**

Q. **I would like to take you to an exhibit that has been put before you by counsel for Allergan. That is PTX-249.**

A. **Okay.**

Q. **Could you remind me very briefly what this, what the**

numbers are in these various columns that are being represented?

A. **This is audit data that shows on a monthly basis total prescriptions in the glaucoma market, and then it breaks it down by key categories and by some of the major brands.**

Q. **And Row 21, that is Alphagan. Correct?**

A. **Row 21 is Alphagan, that's correct.**

Q. **And, just so I am clear, Row 22 is Alphagan P?**

A. **That's correct.**

Q. **And you indicated that Alphagan P came on the market in, let me just follow along here, according to this, it looks like probably late August 2001?**

A. **August, 2001, that's correct.**

Q. **Now, just prior, if we go to Allergan 0905766, and I would like to look at the total unit sales for Alphagan on July of 2001. Please let me know when you have found that portion.**

A. **July of 2001 and Alphagan, Row 21?**

Q. **Yes, that's correct.**

A. **That would be 250,000 prescriptions, approximately, 249,748.**

Q. **Okay. Now, let's look at July 2004. And that's at Allergan 0905770.**

A. **Yes, I have it.**

Q. **And it looks like there is some residual Alphagan**

sales. What is that?

A. **You know, the audit continues to capture prescriptions. It may be things being written as brimonidine. We continue to see ticking of small numbers of sales allocated to Alphagan. Obviously, with no product there, I am not quite sure what that is. It may be product being written as brimonidine .2 percent, captured in the audit that way.**

Q. **This information is not -- there is a certain amount of error --**

A. **Plus or minus a few percent, that's correct.**

Q. **Where is the -- is that a number that you just made up or is that --**

A. **It is what I understand over the years, the audit is just that, it's an audit. It is not a census. It is a projection, methodology, based on, you know, usually capturing data to a certain extent and then projecting it outward. And different audits have different levels of error. But they are very, relatively accurate.**

Q. **Okay. So what is the -- what was the unit volume sale of Alphagan P in July of 2004?**

A. **Alphagan P in July of 2004, that would be -- let me make sure I have the right line here in the report -- Line 22, 215,000 prescriptions for the month.**

Q. **That is less than 250,000. Correct?**

A. **That's correct.**

Q. **And if we go now to April of 2006, which is at Allergan 0905772. What is the unit sale for April 2006 of Alphagan P?**

A. **It's about 180,000 prescriptions.**

Q. **That is less than 250,000. Correct?**

A. **That's correct.**

Q. **Now, I would like to take you back to ADX-16. It was an exhibit that -- could I have ADX-16?**

Now, could you tell me briefly the number on the y axis? What are those numbers?

A. **Those are the monthly prescriptions.**

Q. **So, again, these are unit sales?**

A. **They are not unit sales. They are prescriptions.**

Q. **Actual prescriptions?**

A. **TRx's, total prescriptions.**

Q. **Okay. Now, this August '02 is the date Allergan quit distributing Alphagan. Is that correct?**

A. **That's correct.**

Q. **Now, Allergan told physicians it was pulling Alphagan prior to doing so. Correct?**

A. **Yes. We notified physicians that we would be focusing our efforts on Alphagan P.**

Q. **And, so, if we are looking at ADX-16, physicians knew at this time that Alphagan was no longer going to be**

available?

A. **It was communicated to them publicly that Alphagan was no longer going to be available, that's correct.**

Q. **When you launched Alphagan P, did you tell physicians that Alphagan P was better than Alphagan?**

A. **We provided them the clinical data, and, as I already mentioned, these are fairly savvy individuals, they are well-educated, and, with their experience, they came back and told us that it was a superior product.**

We did point out that, in the clinical data, not only did we have the same level of efficacy with a reduction in the drug, but there was also an advantage in the clinical data on a reduction in allergy.

MR. BENSON: Your Honor, may I approach the Bench?

THE COURT: Yes.

BY MR. BENSON:

Q. **Now, I have handed you a document that has been marked as DTX-192. And this is a memo from a Hans Peter Pfleger. Are you familiar with this gentleman?**

A. **I am.**

Q. **Is he a marketing person at Allergan?**

A. **He is in the global strategic marketing group.**

Q. **Do you oversee that group?**

A. **No, I do not.**

Q. **Do you have any association with that group at all?**

A. **Not directly, no.**

Q. **Do you interact with that group?**

A. **On occasion, yes.**

Q. **Now, I would like to take you to the second page of this document, and there is, at the second bullet point, I would like to direct you to the second sentence of that first paragraph.**

So, isn't it true that ophthalmologists generally have a low rate of switching from a branded to a generic product?

A. **I am not sure if that was true in 1997. It's not true today. That may have been true back when this memo was written, but I can tell you, from the experience that we have had internal at Allergan, and even the example of Cosopt that I mentioned earlier, clearly, that is not true today.**

Q. **I would like to go back to ADX-16. Now, when you launched Alphagan P, you were telling physicians that Alphagan was better -- or Alphagan P was better than Alphagan. Correct?**

A. **We were communicating to them the clinical data which showed of some of the advantages, addressing the concerns that they had with Alphagan, that's correct.**

Q. **You were telling customers, physicians, in this case,**

that Alphagan P was better than Alphagan because it replaced the preservative benzoalkonium chloride with Purite. Correct?

A. **We were communicating to them that the lower concentration was a distinct advantage and that the new formulation had some other changes, including a BAK removed and replaced with Purite as the preservative.**

Q. **And you were telling customers Alphagan P was better because it included electrolytes corresponding with electrolytes found in the human eye. Correct?**

A. **I believe some of the marketing materials did talk about the formulation changes at that time.**

Q. **And as you indicated earlier, you told customers that clinical trials showed that Alphagan P was better than Alphagan. Correct?**

A. **We demonstrated that the clinical effect, the efficacy was equivalent with a reduction in the rate of allergy.**

Q. **And the rate --**

A. **So the word "better" is a very broad statement. What we specifically communicated is what was within the clinical data that we were able to communicate. And that would have been reflected in our promotional materials.**

Q. **Did some of that clinical data relate to tolerability?**

A. **Yes, it did, as it relates to allergy in particular.**

Q. **Mr. Schultz, I have handed you a document identified**

as Defendants' Trial Exhibit 151. This is an e-mail document from Hans Peter Pfleger, who was identified earlier.

THE COURT: 155 or 151?

MR. BENSON: I apologize. DTX-155.

BY MR. BENSON:

Q. Now, I would like to take you to, do you see there are numbers on the lower right? These are Bates numbers. It says Allergan-EX. I would like to take you to EX 0620759. If you could just flip through, starting there and just kind of flip through really quickly some of the pages here. This appears to be a draft of a scientific report intended for publication, doesn't it?

A. Yes, it does.

Q. Okay. And if you look, it says here, right underneath the title -- first of all, let's look at the title. This is a three-month comparison of efficacy and safety of brimonidine-Purite 0.15 percent and brimonidine 0.2 percent in patients with glaucoma or ocular hypertension previously on brimonidine 0.2 percent monotherapy.

Did I read that correctly?

A. Yes, you did.

Q. And it says here, "Author, TBD."

Now, wouldn't you agree with me that "TBD" is to be determined?

A. **Yes, I would assume that.**

Q. **So, at this time -- and at the bottom, this study was supported by Allergan. Correct?**

A. **That's what it appears to say, yes.**

Q. **So, apparently, this advanced draft had not yet had an author identified with it. Correct?**

A. **It would appear that way.**

Q. **I would like to take you back to the very first page of this document. If you look down, there seems to be a second message attached to this one. I would like to highlight that section. It says here, "Attached please find the 3B manuscripts for your review and comment."**

Underneath, it says, "Please note, per the last start com meeting, we have asked Tom Mundorf to author."

MR. MARSDEN: Your Honor, may I interpose an objection. I don't think this is proper cross-examination. There has been no foundation that this witness has seen this document before. In fact, it's from three years before he joined the company.

MR. BENSON: Your Honor, the witness has testified that in marketing the materials, that they provided --

THE COURT: Why don't you establish that he is familiar with this document.

MR. BENSON: Okay.

BY MR. BENSON:

Q. **Mr. Schultz, have you seen this document before?**

A. **I have not.**

Q. **Now, you indicated earlier that when you began work at Allergan, that you investigated the research efforts, the marketing, and other issues relating to the launch of Alphagan P. Is that correct?**

A. **Market research and other historical data. As I mentioned, the strategic global marketing group doesn't report to me. So my team, nor the people that report to me, would be involved with anything that relates to manuscripts. That is outside the sales and marketing organization. It is over in the global and strategic marketing group.**

Q. **Do these individuals provide you with copies of these types of documents?**

A. **No. I have not seen these documents. This would not be circulated within my team.**

Q. **Clinical studies that were sponsored by Allergan wouldn't be provided to you?**

A. **In this stage, where they are being, still being authored in manuscript, et cetera, this would be handled by the strategic marketing group.**

Q. **Now, are you familiar with any of these journals that are described?**

A. **Yes.**

Q. **Advances in Therapy, Journal of Ocular Pharmacology and Therapeutics and Clinical Therapeutics. Do you have any familiarity at all with how Allergan conducts its clinical trials?**

A. **A little bit, yes.**

Q. **Do you have input as to how -- let me rephrase that.**

Does your department ever have input into areas that you would like Allergan to investigate to support your marketing activities?

A. **From a Phase 3 or Phase 3 type manuscript where that falls within R&D, no. For phase 4 type studies, we may meet on occasion with our medical affairs department who conducts those studies, talk about what sort of data needs might be, what we are hearing from clinicians, and they would determine what would be done and what designs and protocols would be completed during any specific year.**

Q. **Would you be surprised to learn that marketing personnel at Alphagan were providing substitute input in scientific journals?**

A. **I wasn't at the company at this point in time. I don't know what the protocol was then. I can tell you what it is now.**

So the global strategic marketing group is involved from a strategic communications perspective. And it's one of the reasons they don't report in my

organization. They are somewhat separate from the day-to-day commercial operation. They are looking at a horizon. They are working closer with R&D and the R&D portfolio products, so they tend to manage that, versus my team and my responsibility handles the day-to-day commercial operations, the sales and marketing products that are currently on the market and available to sell and promote.

Q. Isn't there an ethical issue involved, if scientists are not writing their own journal articles?

A. You know, there have been a lot of debates around the authors of articles and how that is done, et cetera. For this specific article, I don't know. A lot of what I understand inside Allergan, for most of our selections, who the lead investigator of who enrolled the most patients is usually the lead author.

Q. So, you have an understanding of how Allergan identifies lead authors on their papers. Is that correct?

A. As I understand that, from a policy, that generally we go with a lead investigator and/or someone who has enrolled the most patients.

Q. Is this consistent, if you see here, where it says, "Please note, per the last start com meeting, we have asked Tom Mundorf to author," is that consistent with Allergan's policy of identifying authors?

A. It may or may not be. Dr. Mundorf may have been the

lead investigator of enrollment in this trial. I don't know the answer to that. He is an ophthalmologist. I know he has done clinical work and published before for Allergan in terms of the clinical data. He has also done a lot of work on his own and with others. I don't know specifically, as it relates to this data set, why Dr. Mundorf's name is on here. I would suspect it was because he was one of the top enrollers in this clinical study or one of the individuals who helped design and helped the protocol.

Q. **Do you see on the e-mail message whether or not Mr. Mundorf is identified as the recipient of any of these, this document?**

A. **This looks like an internal document, so I am not sure -- Dr. Mundorf would probably have received this under separate cover and be asked to review the manuscript as well at the same time.**

Q. **On the basis of the information -- I apologize.**

A. **And may have been involved before this memo. Once again, this memo is out of context for me. Once again, I do know Dr. Mundorf has published quite a bit in the ophthalmology journals.**

Q. **Mr. Hans Peter Pfleger, is he typically identified as an author on publications that you provide to physicians relating to clinical trials or the clinical experience of any Allergan product?**

A. **Not that I am aware of.**

Q. **Can you recollect at any time Mr. Pfleger being identified as an author on one of those documents?**

A. **Not that I am aware of, no.**

Q. **Is Mr. Pfleger a physician?**

A. **No. He is, as I said, in the global strategic marketing group.**

Q. **Okay. If you go up to the top of this document, if Mr. Pfleger was --**

MR. MARSDEN: Your Honor, I think we are now well beyond anything this witness is knowledgeable about.

THE COURT: That objection is sustained.

BY MR. BENSON:

Q. **One final thing. Alphagan P and Alphagan were being sold at the same time. Correct?**

A. **Correct, for approximately one year.**

Q. **And a physician would distinguish the two when writing a prescription by writing a "P" on the prescription, correct? So Alphagan P as opposed to Alphagan. Correct?**

A. **That was one way to distinguish. They also could have written brimonidine .15 percent. There was more than one way than just writing "P."**

Q. **And Allergan, at the time, informed physicians the necessity of using P or the brimonidine 0.15 percent designation when filling out prescriptions. Correct?**

A. **Yes. If they wanted to ensure the patient got the new improved formulation, they needed to make some designation to avoid confusion and/or callbacks from the pharmacy.**

MR. BENSON: I have no further questions, Your Honor.

MR. MARSDEN: No redirect, Your Honor.

THE COURT: Mr. Schultz, let's take our afternoon break.

(Recess taken.)

THE COURT: All right, counsel. Please take your seats.

MS. BROOKS: Your Honor, we are going to move to the '078 patent, which we haven't addressed yet. That is the Purite patent. Mr. Singer will be doing the direct examination of Mr. Anthony Dziabo.

MR. SINGER: Good afternoon, Your Honor. We call Anthony Dziabo to the stand.

ANTHONY J. DZIABO, JR., having been duly sworn as a witness, was examined and testified as follows ...

DIRECT EXAMINATION

MR. SINGER: May I approach the witness and the Bench to hand out the witness binders?

THE COURT: Yes.

BY MR. SINGER:

Q. **Good afternoon, Mr. Dziabo.**

A. **Good afternoon.**

Q. **Thank you for coming today.**

First things first, I don't want to embarrass you. I understand you have a hearing problem. Is that correct?

A. **That's correct.**

Q. **Unfortunately, is it your left ear. Is that right?**

A. **It's my right ear, the ear that's facing the Judge.**

Q. **You and I both speak loud, you and I won't have a problem, but I wanted to alert the clerk.**

Mr. Dziabo, where are you currently employed?

A. **I am currently employed by a company called Prima Pharm, Inc. out in California.**

Q. **What is your position there?**

A. **I am president of the company.**

Q. **What does Prima Pharm do?**

A. **We are a contract manufacturer of drugs, pharmaceuticals, medical devices, clinical supplies, and also proprietary products.**

Q. **Does that company do business with Allergan?**

A. **We have in the past but not in the recent five years.**

Q. **Are you being compensated for your time here today?**

A. **Yes, I am.**

Q. **How much?**

A. **$300 an hour.**

Q. **Is that your normal consulting rate?**

A. **Yes, it is.**

Q. **Do you have any monetary stake in the outcome of this case?**

A. **Other than a few shares of Allergan stock, no.**

Q. **Mr. Dziabo, could you describe your technical educational background for the Court, please?**

A. **Certainly. I have a B.A. degree in chemistry from Mansfield University in Mansfield, Pennsylvania. I did graduate work in chemistry at Indiana University of Pennsylvania in Indiana, Pennsylvania, not in the state of Indiana. I also did graduate work in chemistry at Cleveland State University in Cleveland, Ohio.**

Q. **Did you earn any advanced degrees?**

A. **I did earn an advanced degree, an MBA from Pepperdine University in Malibu, California.**

Q. **When did you earn that?**

A. **1984.**

Q. **Before working at Prima Pharm, where were you employed?**

A. **I was employed with Medtronic Cardiopulmonary in Anaheim, California.**

Q. **What years was that?**

A. **That was 1997 through mid-2000.**

Q. **And before working at Medtronic, where were you**

employed?

A. I was employed at Allergan, Inc.

Q. How long were you at Allergan?

A. I was at Allergan from 1983 until 1996.

Q. Did your job at Allergan include responsibilities in the antimicrobial field?

A. They did.

Q. Before Allergan, where were you employed?

A. Before Allergan, I was employed by the State Chemical Manufacturing Company in Cleveland, Ohio, and Florence, California.

Q. How would you describe your involvement in ophthalmic products since leaving Allergan?

A. Sporadic at best, here and there. Probably much less than five percent of my total.

Q. Thank you, Mr. Dziabo.

Now, did your job at State Chemical involve responsibilities in the antimicrobial field?

A. They did.

Q. What types of products were you involved with at State Chemical?

A. State Chemical basically manufactured institutional and industrial products. This was a wide variety of different products, including such disparate things as cleaners, degreasers, paints, coatings, floor polishes, hard

surface disinfectants, water treatment products, and a host of other things.

Q. You mentioned the term "disinfectant," which I think everyone in this room has probably used a disinfectant. What did you mean by "disinfectant"?

A. Disinfectant is a system or substance which affects a very quick kill, almost as an event.

Q. Is there an amount of kill that it does?

A. The amount of kill in a disinfectant, you are basically looking for practically total kill. Practically, that usually doesn't happen. So we are talking about kill in the range of 99.999 percent.

Q. Have you worked with other classes of antimicrobial compounds?

A. Yes, I have.

Q. Have you worked with preservatives?

A. Yes, I have.

Q. How can you contrast a preservative with a disinfectant?

A. As I mentioned before, a disinfectant is typically a very aggressive, very powerful type of process which works over a very short period of time, an event, if you will.

A preservative is a process wherein you are trying to prevent biological degradation. In the case of ophthalmics, this would mean biological degradation and

contamination of the ophthalmic products.

That particular process is much less aggressive, and it also has a sustained action over a long period of time.

Q. **Let's break that down a bit.**

Do preservatives kill microbes or bacteria?

A. **They do, but at a very different rate.**

Q. **You mentioned a period of time. How long a period of time are we talking about?**

A. **It depends on the useful, practical life of the product, the intended product. In the case of ophthalmic products, the practical life span is in the neighborhood of two years.**

Q. **Did you become familiar with your work with other classes of antimicrobials?**

A. **Yes.**

Q. **Have you brought with you a demonstrative today, just so we can keep this terminology straight?**

A. **Yes, I have.**

Q. **May I have ADX-18 on the screen.**

Is that that demonstrative, Mr. Dziabo?

A. **Yes, it is.**

Q. **Okay. Just to keep the terminology straight for the day, we have at the top, something called a sterilant. What was the a sterilant in your experience?**

A. **A sterilant is a system or substance which will absolutely, positively, to a very high degree of assurance, wipe out all microbes on the given target.**

Q. **The second bullet is "point in time activity." What did you mean there?**

A. **Again, that is the event, means that it in a very short period of time. The quicker the better.**

Q. **You have, as an example, the use of surgical tools. What did you mean by that?**

A. **Surgical instruments would mean, for instance, something where you would absolutely want to have the highest level of assurance that there were no microbes on that surface to cause subsequent infection in a patient.**

Q. **Makes sense. We have disinfectant. Is that the description you provided before for disinfection?**

A. **Yes, it is. Again, reading bullet point, it substantially kills all the target microbes.**

Q. **We have a new term, "target"? What is target microbes?**

A. **With regards to disinfectant and antimicrobials in general, in many cases, the requirements for testing and substantiating the effect are against a defined panel of organisms.**

Q. **That would be a target organism. Is that right?**

A. **It would be that target organism.**

Q. **Then we see "preservative" down there. Is that your description of preservative from before? Is there anything notable you wanted to add?**

A. **The only thing, again, to emphasize the difference between disinfectant and preservative is that the preservative must have sustained action over a long period of time.**

Q. **Last, at the bottom, what is a bacteriostat, in your experience?**

A. **A bacteriostat is a substance or a system which really doesn't kill any microbes, but it inhibits them from growing and multiplying.**

Q. **Is it used frequently?**

A. **It's used on an event basis frequently because, many times, it gets used up or decays. For example, what we have up here is the sneaker spray.**

Q. **Thank you very much.**

In your experience, were disinfectants necessarily good preservatives?

A. **Not generally so, no.**

Q. **Why not?**

A. **The disinfectant, as we discussed just a moment ago, is a very aggressive, very powerful agent or system. You are looking to basically hit the microbes as hard as you can, as quickly as you can, and eliminate substantially all**

of the microbes on the surface.

Q. Why would that not necessarily make a good preservative?

A. The aggressive nature of the disinfectant could be a problem, especially when you expose those types of agents or systems to, for instance, human tissue, in particular, the tissue and the functionality of the eye.

Q. Okay. Do preservatives necessarily make good disinfectants, the flip-side?

A. The flip-side, that answer would also be no.

Q. Why not?

A. Again, the preservative and its activity must be tailored to, in this case, the tissue in which it will contact. The disinfectant necessarily, does not necessarily have to touch the tissue, but the preservative generally does. So, therefore, you now have to take into consideration the effect not only on the microbes but on the target tissues or the tissues that will come in contact with the solution.

An example of that would be a sorbic acid, which is a well-known ophthalmic preservative. It would never be able to meet disinfectant criteria.

Q. Are there recognized standards for disinfectants and preservatives?

A. In the case of ophthalmic products, indeed, there are.

Q. **Where are those found?**

A. **Those are basically the responsibility of the FDA. For instance, for preservatives, the FDA references the USP.**

Q. **What is the USP?**

A. **The USP stands for the United States Pharmacopeia.**

Q. **If you could turn to, you should have a binder in front of you, and you should have what's been marked as Joint Exhibit 79 in front of you. Can you identify that for the Court, please?**

A. **Yes. This is the title page from the 1985 volume of the USP, Volume No. XXI. It also contains the national formulary, the NF, Volume 16.**

Q. **Are there standards for preservative efficacy in this document?**

A. **Yes.**

Q. **Where are those?**

A. **If you page down, you will come to --**

Q. **There are little references at the bottom.**

A. **Allergan 0979233, please.**

These are the general chapters in the USP, as you can see, the heading, Microbiological Tests, Chapter 51, this describes the process and the requirements for antimicrobial preservative effectiveness testing in the USP 21.

Q. **Generally speaking, what are those requirements?**

A. **Those requirements, basically, are that the target organisms, the bacteria, are reduced to 99.9 percent in the initial concentration, by the 14th day, and, actually, you can highlight that, it's on the second column, just above Chapter 61, and, so, it's .1 percent in the initial concentration or a total kill of 99.9 percent by the 14th day. And the concentrations of the yeast and the molds remain at or below during the first 14 days and then neither the bacteria nor the yeast nor fungi grow any further until the 28th day.**

Q. **And how is that different from the USP tests for a disinfectant?**

A. **There is not a USP test for disinfection, the, in the case of contact lens care, where we are going to be talking about disinfectant, but there are guidelines published by the FDA that say, here are the standards for disinfection.**

The FDA will very, when it can, refer to the USP, where possible, where there is a test that covers the particular situation. Where the USP is lacking, it will promulgate its own regulations and standards.

Q. **My apologies for my mistake. How does that test that we just saw differ, generally speaking, from the disinfectant test you just referenced?**

A. **In the disinfection tests -- I am sorry, I misinterpreted you there -- the disinfection test basically**

requires a kill on a very, very short time frame, usually in the minutes or hours time interval.

Q. **Thank you.**

Could you contrast your experience at State Chemical with your experience at Allergan in antimicrobials for the Court?

A. **Yes. At State Chemical, our business was, as I said, institutional, industrial. We were selling to hospitals, nursing homes, those types of institutions. Their requirements for disinfections were what I will call hard surface disinfections, tabletops, door mats, bannisters, walls, floors, ceilings. Those types of situations.**

The latitude we had in that situation, sometimes I describe it as, is that tabletops don't scream. So you have the ability to use overwhelming force, if you will, on those inanimate objects. Your only requirement is that you don't dissolve the object that you are trying to work on. You had the ability to bring, like I said, overwhelming force to bear on those particular assignments, if you will, those typical uses.

Q. **I take it you could not do that in ophthalmics. Is that correct?**

A. **In ophthalmics, you now have a situation where, as we talked about previously, the preservative is more than likely going to find its way into the eye. Obviously, the**

eye is a very, very sensitive organism. The issue you are always dealing with here is one that I call friend versus foe.

Most of the preservatives in the marketplace can't tell the difference between a pseudomonas organism, which can cause infection, and the corneal epithelial cell. It works the same on both.

So you have a problem in that your formulation must take into consideration the fact that you have to balance, you have a balance point where you have to have enough antimicrobial activity, but you have to also make sure that you have not exceeded the toxicity standard or toxicity requirements for the eye.

So, it's a balancing act. It's sort of like a teeter-totter situation between activity and toxicity.

Q. **Thank you, Mr. Dziabo.**

Let's talk more specifically about your work experience at Allergan. I think you testified you joined the company in 1983. Is that correct?

A. **That's correct.**

Q. **What was your first position when you were hired at Allergan?**

A. **I was hired as a formulation scientist in the contact lens, hair product area.**

Q. **We have heard formulation at this trial. Did you work**

on the formulation with active ingredients at Allergan?
A. I take it by "active," you mean active pharmaceutical ingredients?
Q. Yes, that's what I mean.
A. Okay. At that time, no.
Q. Did you stay a formulation scientist during your time at Allergan?
A. No. I progressed with increasing responsibilities from scientist to managing scientist to managing scientists who managed scientists, to managing different departments, et cetera, until, finally, I was the vice president for R&D of the optical group.
Q. Getting to the time frame that is relevant to this case, which is roughly 1983 to 1988 or '89, what was your position then?
A. I was a manager of the formulations group.
Q. Did you manage a person by the name of Mr. Paul Ripley?
A. Yes, I did.
Q. Who is Paul Ripley?
A. Paul Ripley was a formulation scientist working in the same division as myself.
Q. Did he, in fact, start at Allergan on the exact same day you did?
A. Yes. In fact, he and I both started on the very same

day.

Q. Did you work closely with Mr. Ripley?

A. I did, indeed, work in that time frame very closely with Paul. He reported directly to me.

Q. Mr. Ripley and you are the inventors on the patent that Ms. Brooks referred to. Is that correct?

A. That is correct.

Q. What were your responsibilities in the antimicrobial field at the time you joined Allergan?

A. Can I get a glass of water?

Q. Absolutely.

A. Would you please repeat that last question?

Q. Sure. I just am referring you back to the time you started at Allergan in 1983.

What were your responsibilities at the time you joined?

A. My responsibilities at that point in time were to look for new antimicrobial agents to use in improving our existing contact lens disinfection products.

Q. Did you have a particular approach that you were pursuing at that time?

A. Yes. What I conceptualized as my approach at that point in time was that the existing products in the marketplace, I felt had one -- had several serious drawbacks. That is these disinfecting agents, these

powerful chemical agents, all found their way back into the eye, hitching a ride on the contact lens.

When a patient wore contact lenses, they would remove the lenses at night and they had to store them in something. And they had to disinfect them because the lens could be contaminated by handling, by the environment. So the next morning, they wanted to have a basically microbe free lens to put back in their eye.

The problem was is when you soak those lenses in such a solution, the active agent hitched a ride back into the eye, if you will.

Q. **What was your idea for solving this kind of problem?**

A. **I wanted to get the active agents out of contact with the eye.**

Q. **What approaches were you pursuing at the time you joined Allergan or after you joined to try to get the agent out of the eye?**

A. **I was looking for chemicals or systems which would, as I characterize it, disappear by the time the lens got into the eye.**

Q. **What do you mean by "disappear"?**

A. **That the agent was either neutralized, it was bound, it was changed in some way so that it did not exhibit the non-discriminate activity, or it had dissipated.**

Q. **Were there particular approaches that you were**

pursuing to make these agents disappear?

A. **Yes, there was. We had hydrogen peroxide systems, for instance.**

Q. **How did those work?**

A. **Hydrogen peroxide, three percent hydrogen peroxide we were using as a disinfectant, a very powerful antimicrobial agent but you couldn't put it in the eye, it was very toxic. The useful thing about hydrogen peroxide is we had agents that we could add in and destroy the hydrogen peroxide to water and to oxygen, to harm less substances in the eye. That was one approach.**

The other approach we had, too, is we built upon some previous custom or practice in contact lens wear, which was the heaters.

Q. **What were you doing with the heaters?**

A. **If I can explain a moment, the heater was basically a way to disinfect a contact lens. Basically, you took the lens out of your eyes, you put them in a lens case with saline, the lens case was put in a little device that was about yeah by yeah, you turn the button and it would heat it up and you basically boiled the lenses. That affected the disinfection.**

The problem with that was all of the debris on the lens from the tear film, all of the deposits, et cetera, et cetera, got baked onto the lens. And you had this

lasagne of deposits, layers, in many cases, of deposits on the lens, which, when the patient would put on their eye, would cause conjunctivitis.

So heaters were, you know, somewhat suspect. What we did is we adapted the process. We changed the active agent from heat to chlorine gas.

Q. **How did you go about doing that?**

A. **Well, we used the same saline, because saline has sodium chloride in it, as the tonicity agent. And now, instead of heating it up, we basically ran a current through the saline and it generated chlorine case. Chlorine gas is a powerful micro biocide. It then completed the disinfection. But the nice thing about that was the chlorine gas is volatile, and it de-gasses out of solution, so we made the antimicrobial disappear.**

Q. **And that was through an approach using a gas. Is that correct?**

A. **That was an approach using a gas, chlorine gas in this case.**

Q. **During the time you were doing this work with gaseous antimicrobial agents, did you learn of a company named Bio-Cide?**

A. **I did, because one of my assignments and one of our approaches was we were casting a very wide net to find all of the different types of antimicrobial agents available**

throughout the world. And I came cross an information packet from Bio-Cide Chemical.

Q. I would like to show you in your binder the next tab, it's Joint Exhibit 83.

Do you have that, Mr. Dziabo?

A. I do.

Q. Is this the material you just referred to as coming across from Bio-Cide?

A. Yes, this appears to be part of it, yes.

Q. Okay. If we could blow up at the bottom of the front page, it says Bio-Cide Chemical Company, doesn't it?

A. That's correct.

Q. What caught your eye about this patent?

A. Several things. If we can go right up to the first line, you can see there, it says, "Chlorine dioxide is a gas."

Q. Why did that catch your eye?

A. Well, because of the second sentence on there, too, actually, I guess it's the fourth sentence, it says it's very volatile.

Q. Why was that important to you?

A. Again, like our chlorine gas product, volatile gas meant that it would dissipate from solution and disappear.

Q. Was it also a known antimicrobial agent?

A. Chlorine dioxide had been known for some time. The

other thing that attracted us, and myself, to this concept was that chlorine dioxide had been used in water treatments. So there was a great deal in the literature concerning its systemic toxicity.

Q. Looking down at the first paragraph, referring your attention to the bottom, what was the approach Bio-Cide was advocating in this patent with respect to utilizing chlorine dioxide gas?

A. Well, basically, they represented that they had a stabilized chlorine dioxide product which they could use as a chlorine dioxide generating system.

Q. Where do you see that --

A. Well, it's in a couple spots there. Down a couple lines.

Yes, that's the sentence. That's good.

Q. It says, "Several years ago, a method was developed to stabilize the chlorine dioxide gas into an aqueous alkaline solution - thus the term 'stabilized chlorine dioxide'."

Is that what you were referring to?

A. Yes.

Q. Where does it say it generators chlorine dioxide gas? At the time bottom there?

A. At the very end of the paragraph.

Q. If we could highlight the last sentence. What does it say there?

A. **"The solution is a CLO2," excuse me, sometimes I will say chlorine dioxide, sometimes CLO2, but "a chlorine dioxide generating system which produces the chlorine dioxide molecule in a spontaneous manner."**

Q. **The chemical name they gave to this was what?**

A. **The stabilized chlorine dioxide.**

Q. **I want to refer your attention to the top. If we could go to the top of the paragraph, Mr. Exline, you said it was very volatile. But it also says it was explosive at concentrations above ten percent in the air?**

A. **Yes.**

Q. **Did you have a memorable experience with a gas in your lab about the danger of chlorine dioxide?**

A. **Yeah. In fact, we did. Paul Ripley, who, again, worked on this particular project, when he was early on working with some of the stabilized chlorine dioxide samples, inadvertently released a cloud of the chlorine dioxide gas. And he kind of did it on a bench, he says with a knockout punch. He said he basically staggered, had to get himself fresh air, and had to go sit on a curb for a while until he cleared his head.**

So, yes, it was a very powerful, aggressive chemical agent.

Q. **If this gas is so powerful, why were you interested in working with it in ophthalmics?**

A. **Again, I was looking for agents that met the definition of disinfection, that is, is powerful, aggressive, quick-acting. But, also, I could disappear them, if you will.**

Q. **How did you envision using the Bio-Cide product?**

A. **I was thinking about a system in which we could use the stabilized chlorine dioxide, and, on demand, or, at the appropriate point, release the chlorine dioxide, obviously, in much lower quantities than Paul Ripley had in his little incident. And I felt that because of its enormous ability for antimicrobial activity, could affect disinfection in a very quick and thorough manner.**

Q. **What pH does the brochure say the product came with? If I could help you, Mr. Dziabo, I will refer your attention to the second page, first paragraph.**

A. **073057, Mr. Exline, the first paragraph, can you see it there, at about the fourth sentence? Actually, the fifth sentence, I am sorry.**

Q. **Fifth line?**

A. **Fifth line, I am sorry. Fifth line.**

Q. **If we could highlight the fifth line, "The concentration is maintained at a" --**

A. **A pH of 8.5 to 9.0.**

Q. **Was that a concern for you?**

A. **Yes, it was.**

Q. **Why?**

A. **That pH is outside the range of the native pH of the eye.**

Q. **What did Bio-Cide say in this brochure would happen when you dropped the pH?**

A. **That they would, at that point, liberate the chlorine dioxide gas.**

Q. **Did the packet have any data regarding toxicity of the substance?**

A. **It did. Mr. Exline, I think that's back a bit further. Allergan 0730578.**

Q. **What is this, Mr. Dziabo?**

A. **This is a report of a toxicity test that was run on the Purogene, which, my understanding was the brand name for the stabilized chlorine dioxide product from Bio-Cide.**

Q. **In fact, it actually has two brand names in the front of the page. Is that right? It was Purogene and Oxine, if we could just quickly see that on the first page?**

A. **Yes. There were several names that were used in the offering. I believe, I am not sure, but I believe it was because they had different target markets, and, so, Bio-Cide labeled them differently.**

Q. **Let's talk about this toxicity test. It's called a Biological Report of Analysis from the United States Environmental Protection Agency. True?**

A. **That's correct.**
Q. **Okay.**
A. **Excuse me. No. It's on a form approved by the Environmental Protection Agency. This was not done by the Environmental Protection Agency.**
Q. **Thank you for clarifying that. My fault.**
What does it say the active ingredient in Purogene is?
A. **On Section 11 there, if we can pop that up, it says chlorine dioxide two percent.**
Q. **Then it provides a test right below that, if we could blow that up?**
A. **Right. If you look at the line that starts with 12, 13, and across, there is 14, 15, 16, 17, the type of test was an ocular irritation screen. If you look over at No. 14, it is a modified Draize test.**
Q. **What was your understanding as to what a Draize test was?**
A. **A Draize test is typically a test that is required to simply determine what the danger would be to a user if the product was accidentally splashed into the eye.**
Q. **Is this a chronic test like one would use in an ophthalmic product?**
A. **No. That is one of the real shortcomings from this type of data. From an ophthalmic perspective, this is a**

one-time installation. So it is an event, it is not something that gives me any information on the use of a product for many, many months or even years.

Q. **How relevant to your work at Allergan was this information?**

A. **Not very relevant at all.**

Q. **What do the results say?**

A. **The test basically was two albino rabbits. They put a couple drops into each of the rabbits in the eyes. One of the eyes was washed out, the other was left unwashed. The rabbits are typically, in this type of a test, are watched for seven days to see what happens. In other words, the eyes are examined on a regular basis over seven days. And there is a method for storing the product and its toxicity.**

As you can see, their conclusion in this laboratory was that the product was only a slight ocular irritant causing mild conjunctivitis in both eyes, the one washed, the one unwashed eyes of the two rabbits tested.

Q. **Was this a problem for you?**

A. **It caused a lot of concern in that if this was one installation, and, in fact, in one case, it was washed out of the eye, this was a washout for us in terms of toxicity because, in ophthalmic products, we are going to be putting this in peoples' eyes at least on a daily basis.**

Q. **Why did you decide to persist in looking at the**

Purogene product?

A. **It still had many of the requirements that I had conceptualized for the design of an advanced disinfecting system.**

Q. **This was the gas faced approach you were talking about?**

A. **The disappearing antimicrobial, yes.**

Q. **So what did you do? You read this packet. What did you?**

A. **I, basically, at that point in time, wrote a letter to Bio-Cide.**

Q. **We can pull up a letter for you at PTX-2. What are you requesting in this letter?**

A. **This was a letter where I basically say, I have seen your packet of information. I am interested. And we would like to see some samples, both liquid and -- we would just like to see some samples.**

Q. **What happened after that?**

A. **We received a visit from Mr. Bob Danner.**

Q. **Who is Mr. Bob Danner?**

A. **Bob Danner was then the president of Bio-Cide.**

Q. **Did Mr. Danner come out to Allergan?**

A. **Yes, he did.**

Q. **Did he meet with you?**

A. **Yes, he did.**

Q. **Was there anyone else at that meeting?**

A. **I can't exactly recall who all was at that meeting. It's been a while.**

Q. **What do you remember about that meeting?**

A. **I remember about the meeting that Bob was a very polished individual. He was very excited at getting a contact from Allergan. And he was very much in a salesperson mode.**

Q. **What do you mean by that?**

A. **Well, he wanted us to move forward with all haste and with all of our, you know, resources, to put the product, based on his materials, on the marketplace.**

Q. **Understandably.**

Did he send you the samples that you requested in Plaintiff's Exhibit 2?

A. **Yes, he did.**

Q. **If you could turn in your notebook to Exhibit 207. If we could put that on the screen. Defendants' 207.**

Is this a letter you received from Mr. Danner following the meeting?

A. **Yes.**

Q. **Does this enclose a sample of the product?**

A. **Well, he sent it under separate packet, yes.**

Q. **What product is he sending you?**

A. **Well, this was a one thousand part per million of the**

aqueous chlorine dioxide solution, as he characterized it.

Q. Why is there a lower concentration than we saw before, the two percent?

A. Because during our conversations, we talked about approaches with regards to developing products, and those approaches included things like looking at different concentrations so we could define the antimicrobial activity at different concentrations, we would then subsequently define the toxicity at different concentrations, and, really, learn to understand the physical properties and the performance properties of these antimicrobial agents.

And in this case, we talk about, I am sure we talked about the 1,000 ppm, probably due, in large part, to the toxicity data we had seen with the two percent solution previously.

Q. The letter at the bottom says there are eye toxicity data included. Do you see that?

A. Yes.

Q. What do you remember about that?

A. He did send along additional toxicity data that he had on file at that time that wasn't in the previous packet.

Q. Was it the same type of data, the Draize type data that you recall?

A. Yes, if I recall, it was Draize testing again.

Q. Did you eventually receive the sample?

A. **Yes, we did.**

Q. **Did you receive other samples from Mr. Danner thereafter?**

A. **Yes, we did.**

Q. **If you could turn to Defendants' Exhibit 189. Do you have that in front of you, Mr. Dziabo?**

A. **Yes, I do.**

Q. **Can you identify this document for the Court?**

A. **Yes. This is a letter from Great Plains Laboratory to myself, talking about the samples that were being prepared.**

Q. **And what concentration are the samples?**

A. **200, 500, and 1,000 ppm.**

Q. **Drawing your attention to the top line of the letter, it states, "The enclosed samples of Purogene are very near the correct osmolarity, although we have no way to actually measure the actual value for each."**

What do you understand that to be referring to?

A. **Well, as part of the conversations we had with Bob Danner, we brought up several points, including the concentration. There were two other main attributes that we were very concerned with, one of which was the pH. You had mentioned earlier, we looked at earlier the fact that the stabilized chlorine dioxide had a pH of 8.5 to 9.0. That would be unsuitable for on ophthalmic product. So we asked him about addressing the pH.**

We also asked about the osmolarity. Osmolarity is a measure of the tonicity or the solute in solution, and that's a basic property of the eye. So, the pH, you want to match up everything with the native eye. You don't want to color outside the lines there, because that can cause problems. So we also talked about tonicity values and samples with the correct tonicity. And this was -- and Bob said, I will have my laboratory prepare those for you, as we discussed and targeted.

The other thing that is kind of interesting about this is that the laboratory that he used, which Bob represented as his right-hand man, so to speak, had no way to measure osmolarity.

Q. **What does that mean?**

A. **They did not own an osmometer.**

Q. **Did that surprise you?**

A. **It did surprise me for somebody who was attempting to work in the ophthalmic area.**

Q. **Did Mr. Danner send you any further toxicity information around this time?**

A. **Yes, he did.**

Q. **Refer your attention to the next exhibit in your packet. It's in there as Defendants' Exhibit 213.**

Do you have that in front of you, Mr. Dziabo?

A. **I do.**

Q. **Can you identify this letter for me, please?**

A. **This was a memo back from Bob Danner to myself concerning a phone call that we had. I am sure that our discussion here was one of which is, again, toxicity data. And he was informing me that he had recent, the most recent toxicity data on a product called Oxine, which he was going to forward to me.**

Q. **Oxine, that was the same as Purogene?**

A. **My understanding was it was the same fluid, same liquid, different name.**

Q. **I see there is enclosures. It says, Still Meadow Toxicity Studies. Do you see that?**

A. **That's correct, yes.**

Q. **Did you receive those Still Meadow Toxicity Studies?**

A. **Yes, we did.**

Q. **We have marked as Defendants' Exhibit 348 in your binder a document. If you could take a look at it.**

Is this one of the Still Meadow Toxicity Studies?

A. **Yes, it is.**

Q. **Is this one of the documents you received from Mr. Danner through Defendants' Exhibit 213?**

A. **Yes, it is.**

Q. **What about kind of information is in this Still Meadow Toxicity Study?**

A. **Well, the best way to digest this is go to, Mr. Exline, if you go to Bio-Cide 0000742, there we are, which talks about the study summary.**

Q. **Is there a particular portion that we should be focusing on, Mr. Dziabo?**

A. **I would like to highlight a couple things.**

Number one is that this study was conducted with nine rabbits. If you remember, the previous study was with two. That's back in the body a little bit -- actually, it is defined right here, nine albino rabbits.

If you go to the third paragraph, basically, the procedure was one-tenth of a milliliter. There are 20 drops in a milliliter, so one-tenth of a milliliter is going to be two drops. So two drops of the undiluted test material was placed into the conjunctiva of, the left eye of each rabbit. Several of the eyes were washed. Several of the eyes were left with the fluid in them. Then the rabbits were observed for seven days.

So this, basically, is a repeat of the Draize test that we saw previously with nine rabbits instead of two.

Q. **How relevant was it to your work at Allergan for optomic products?**

A. **Again, this was destined to give information on accidental exposure, accidental one-time exposure. And it**

was not very relevant with regards to a chronic ophthalmic product which would be used repeatedly over and over again.

Q. Again, Oxine and Purogene are one and the same, as far as you understood?

A. That's correct.

Q. What you did you understand to be some of the other commercial marketed use of Oxine?

A. Bio-Cide, basically, would sell this at any situation where disinfection or odor control was necessary. They had, I know, labeling that talked about most every hard surface disinfection that you could do, ice machines, floors, walls, our famous swine pens and animal holding pens and chicken barns, dairies, for cleaning the floors. Basically, they had a very, very broad target. That's their prerogative, and the product worked in many of those situations.

Q. I didn't mean to cut you off.

A. I am sorry. So, you know, there was a myriad of uses, but most of these uses were like our hard surface disinfection that we described earlier.

Q. If you could turn in your binder to Plaintiff's Exhibit 626. Can you identify what this document is?

A. Yeah. This is the approved labeling, the approving agency is the United States Environmental Protection Agency, and package insert for Oxine.

Q. Is this labeling consistent with your understanding of

the commercial product?

A. **Yes. This basically gave all sorts of directions for use in these areas that we just discussed.**

Q. **Does it give a warning about contact with the eyes?**

A. **Yes, absolutely. If you look down here, under the "Caution" statement, it says, Avoid contact with the eyes.**

Q. **And I want to refer you to Page 7, because you mentioned it. At the top of the page, it suggests the product be used to disinfect commercial animal confinement facilities, such as poultry houses, swine pens, cat barns and kennels. Did I read that correctly?**

A. **Yes.**

Q. **Is that what you were referring to before?**

A. **Yes.**

Q. **Mr. Dziabo, I am sure everyone in the courtroom is wondering, why were you thinking of putting this product in peoples' eyes?**

A. **Well, first of all, I felt that we had to look outside the realm of what was accepted and generally available for ophthalmic products if we were going to come up with new products. The old story of insanity, you know, doing something over and over again and expecting a different result. If we wanted to have a different product with different attributes and solve the existing marketing and performance problems, we needed to look exhaustively and at**

all different types of concepts. Again, I was very interested in this material because I could make the active agent disappear at some point in time.

Q. **That was through the gaseous approach which you described?**

A. **That's correct.**

Q. **Thank you, Mr. Dziabo. We can pull that down.**

You have the samples, the 100, 500, and 200 in the door at Allergan. You have gotten some limited information from Mr. Danner.

What was the next step, or the first step you took at Allergan with respect to developing this product further?

A. **The next step would be to look at its toxicity profile. Obviously, with all of the information, as you just pointed out, the first step would have been, wait a second, is this stuff ever going to be able to be used in the eye? What really is the toxicity profile if we want to tee it up for the eye?**

Q. **I would ask you to turn to the next tab in your binder at Joint Exhibit 84. Do you have that, Mr. Mr. Dziabo?**

A. **Yes, I do.**

Q. **What are we looking at here?**

A. **This is a, I think, a project report or a monthly report of activities in our toxicology group.**

Q. **And did any of this information refer to Purogene?**

A. **Yes. If you go down and look at Items 10, 11, and, on the back side, 12.**

Q. **What kind of tests are these?**

A. **These are specific tests that Allergan used, and, in many cases, developed the regimen. We had a dedicated toxicology group as part of our R&D resources, which was very useful to us, because these people, they were just absolute experts in testing products for ophthalmics, and they were in-house, so we had direct access to them.**

Item No. 10 here, this is an acute high toxicity and cytotoxicity study on 1,000 ppm Purogene in conjunction with the Permalens soft contact lenses.

Q. **How does this differ from the Draize test that we saw before?**

A. **It differs in several very significant ways. The biggest one being that if you -- that we used a contact lens in conjunction with the solution. And, basically, what this study does is that you soak the lens in the solution, overnight, like a patient would, then they take the lens out and put it on a rabbit eye. We had skillful technicians that could get contact lenses directly onto the rabbit. Then we would put drops of the solution in the eye during the day to sort of take the first step look at, Well, what happens in a rabbit eye, in the rabbit eye model?**

Q. **Now you are at the lower concentration now, 1,000 ppm?**

A. **That's correct.**

Q. **And that's, if I do my math, 120th of the original concentration information you had. Is that correct?**

A. **That's correct.**

Q. **Okay. What were the results of these acute eye toxicity and cytotoxicity studies?**

A. **If we go back, Mr. Exline, to Allergan 0971177.**

Q. **May I suggest, Mr. Dziabo, you look at the page prior. I am looking at that. It is a conclusion.**

A. **I went too far. I am sorry. I went too far. Yes. The first one corresponds to 1175, I am sorry.**

Q. **If we could look at the conclusion in that document on 0971176.**

A. **Hold on a moment. I think Mr. Exline has to catch up with us.**

Q. **One more forward, 0971176.**

What is the conclusion of this toxicity study?

A. **Basically, we found that the regimen was slightly irritating but not discomforting, toxic, or cytotoxic in rabbit eyes.**

Q. **Are you okay?**

A. **Yes. Cytotoxic is just a terminology meaning toxic to cells.**

Q. **Mr. Dziabo, let's look at the conclusion again. What**

are the results of this toxicity study on the 1,027 ppm Purogene?

A. **It was slightly irritating but not discomforting, toxic, or cytotoxic to rabbit eyes.**

Q. **Was this a concern to you?**

A. **Can we take a small break. Because it is not clearing up.**

THE COURT: Let's take a stretch. Thank you.

(Recess taken.)

MR. SINGER: Thank you, Your Honor.

BY MR. SINGER:

Q. **Before we broke, Mr. Dziabo, we were talking about Joint Exhibit 84. The conclusion we have up on the screen. I had asked you, were the results you got that Purogene was slightly irritating a concern to you?**

A. **Yes, they were, because this was one cycle, if you will. In other words, one overnight soak, one application to the lens, one day. And, obviously, a contact lens, the patient is going to wear their lenses every day for years.**

Q. **Was this also a much more dilute concentration of the product?**

A. **Well, this was a dilute -- this was the 1000, nominally, ppm concentration. So the issue here was that if this happened one day, is there a cumulative toxic effect at 1000 ppm.**

Q. **Did your group also conduct antimicrobial tests around this time?**

A. **Yes, we did. That's part and parcel of the evaluation of these types of products. As I mentioned previously, looking at the toxicity profile versus the antimicrobial profile at various concentrations and solution conditions.**

Q. **Who were you working with on this project?**

A. **I was working with Paul Ripley at that time.**

Q. **If you could turn to the next tab in your binder, which is Joint Exhibit 85. Do you have that in front of you?**

A. **I do.**

Q. **TWEL actually, if you would look at the back pages of that, not the front memo page, but Allergan 971234 and Allergan 971235. Do you have those?**

A. **Yes, I do.**

Q. **Whose handwriting is this?**

A. **This is Paul Ripley's handwriting.**

Q. **What experiment is he running here?**

A. **This is a antimicrobial evaluation. As you can see in the upper right-hand corner, an experiment, that is an experiment number, it is not real legible, it is 7162. That was just a sequential number assigned to experiments in microbiology.**

What he was looking at here was that he was

testing various concentrations of the Purogene, if you can slide down a little there, Mr. Exline, and highlight that.

Q. **You are referring to the methodology?**

A. **Yes.**

Q. **What are the concentrations of Purogene being tested?**

A. **In this case you can see that there are basically five different samples. And you have Purogene A, B, and C. Purogene A being .1 or 1000 ppm. B being . 05, 500 ppm, and C being .02 or 200 ppm.**

Q. **Were these the three solutions you received from Bio-Cide?**

A. **Yes.**

Q. **And then there are two more solutions, 383 and 384. What are those?**

A. **These are controls. The 383 is Allergan Hydrocarina disinfectant solution, which was the Allergan soft lens disinfecting solution which had been used previously in the marketplace. And it consisted of S. marcescens and proterium (phonetic) as the disinfecting system.**

Q. **What is 384?**

A. **That is a product called Lesandt A, which was a three-percent hydrogen peroxide.**

Q. **There are some results at the bottom of the page. And there are lots of numbers and pluses. I would like to try to explain this for the Court. What are we looking at? And**

we will just try the first row. Where are we looking at there?

A. **The far left-hand row, this is the test organism.**

Q. **What is the organism here?**

A. **The organism, the first organism in the first box is Serratia marcescens. I realize that is very hard to read. I happen to know that because that is a standard target organism that we test against. Remember, we talked about typical target organisms.**

Q. **Okay. Then it says initial 6.7 times 10 to the 5th. What does that mean?**

A. **Well, it also says CFU per milliliter. That is colony-forming units per milliliter. Basically, what that means is you got 6,700,000 Serratia marcescens organisms per milliliter in that sample.**

Q. **Then there is a time column. What does that refer to?**

A. **That is the time at which samples are taken for assay to determine how many microorganisms remain after the addition of the antimicrobial solution.**

Q. **Then we have the five different samples tested, 380, 381, 382. The first three are Purogene. Correct?**

A. **That's correct. And I believe in the order of 1000, 500, 200, declining concentration as we move to the right.**

Q. **What are the results for the 1000 ppm solution?**

A. **For the 1000 ppm solution, you can see, after five**

minutes of testing, that basically there are no microorganisms left. Well, I am sorry, they were able to find about a hundred microorganisms, less than a hundred microorganisms. Basically they can't count. That is too small a number to count. That is why you see at ten minutes the less than 10 to the 2 sign. That basically means all the microorganisms are gone.

Q. **What about the 500 ppm?**

A. **The 500 ppm shows less activity. You can see comparison at the different time points, at no time point do we get the total kill, that is the less than the 10-to-the-2 organisms.**

Q. **How about the 200 ppm?**

A. **The 200 ppm is even worse. Compare, for instance, 15 minutes across the board for the 1000, there is none left. But for the 500, now we have two times 10-to-the-three, and for the 200 it's six times 10 to the 5. Basically, no change from the initial concentration.**

Q. **Now, there are other target organisms in this experiment as well?**

A. **Yes, there are. They follow a similar pattern.**

Q. **Overall, what were the results for the 200 ppm Purogene?**

A. **They re pretty poor for the time frames we are looking at here.**

Very little activity against the bacteria. The first three organisms listed here, which are the Serratia marcescens, the S. aureus, and the Pseudomonas aeruginosa. Pseudomonas aeruginosa is a very bad player and one we watch very carefully because it is implicated in many eye infections.

Q. **What are the results for the 500 ppm? I am sorry. Just across the board, across the spectrum of the agents?**

A. **The 500 ppm is better than the 200 but less effective than the 1000.**

Q. **What are the results for the 1000?**

A. **The 1000 are excellent against the bacteria. As I was mentioning, the first three organisms were bacteria. The fourth organisms in sequence is Candida albicans, or C albicans, which is a yeast. And the last organism is A. niger, or Aspergillus niger, which is a fungi.**

Q. **What was the activity against the fungi?**

A. **The activity against the fungi was absolutely nonexistent for any of the concentrations.**

Q. **I would like you to turn to the first page of Joint Exhibit 85 and ask you to describe the experiment in this memorandum?**

A. **This is basically the same experiment, except now we are looking at differences in pH. In this case, we tested .1 percent Purogene or 1000 parts per million of Purogene at**

7.3, 8.2, and 9.2 pH.

Q. **What were the results?**

A. **The results were very similar to the experiment that was done that was shown previously in Paul Ripley's notebook. And, again, the 1000 ppm lacked activity against the fungi.**

Q. **That is referenced in Paragraph 3?**

A. **That's 3, yes. Spores -- they are a little loose with their terminology here -- fungal spores, spores in general.**

Q. **It says chlorine dioxide. That's consistent with the gas generation approach that Bio-Cide told you about?**

A. **Well, what's happening here, this is the Purogene 1000 ppm. It stabilized chlorine dioxide.**

Q. **What did you understand the active ingredient in Purogene to be at that time?**

A. **That was represented as chlorine dioxide.**

Q. **Based on these results, would it have been suitable to use Purogene as a disinfectant?**

A. **It was looking pretty grim for Purogene-stabilized chlorine dioxide as a disinfectant.**

Q. **Did you try anything like upping the concentration to see if it would work?**

A. **Yes, we did.**

Q. **Can I have you turn to the next document in your binder, PTX-579. What is this document describing?**

A. **This is a report to Paul Ripley from our microbiology department concerning a test, an evaluation of Purogene 2 percent, 1 percent, and .1 percent.**

Q. **.1 percent is a thousand ppm?**

A. **.1 percent is a thousand ppm.**

Q. **And two percent is the full two-percent solution?**

A. **By comparison, 20,000 ppm.**

Q. **And what were the results of this experiment?**

A. **This experiment was set up to test just the yeast and the fungi, because we were pretty confident of the activity against the bacteria. So we really didn't need to re-test that.**

The issue, the sticking point, was the fungi in the yeast. The results are probably -- let's see, if you look at Item No. 1 here in the summary --

Q. **What does that say?**

A. **Increasing the concentration from .1 to 2 percent increased the activity against the Candida yeasts -- there were two Candida yeasts used in this instance -- and A. fumigatus spores, that's Aspergillus fumigatus, but showed no change in the activity against A. niger.**

Q. **Would you characterize this experiment as a failure?**

A. **In the context of disinfectants, yes, we still weren't getting any activity against A. niger.**

Q. **By this time were you starting to understand more**

about the chemistry in Purogene?

A. We certainly dug into it to a greater degree.

Q. What was your understanding at that time as to what was in the bottle?

A. What was in the bottle was a solution of stabilized chlorine dioxide that would release chlorine dioxide upon demand as needed for disinfection.

Q. Upon investigating what actually was in the bottle, what did you learn the constituents of Purogene to be?

A. Well, in looking at the chemistry and what we could find in the literature concerning the chemistry of chlorine dioxide, one of the things we noticed was the presence of a chloride molecule --

Q. I am sorry. Did I cut you off?

A. Yes.

Q. I am sorry.

A. So we decided to do some analytical chemistry comparing the purity to the other possible constituents of the stabilized chlorine dioxide solution. I don't know if I said that correctly.

We tried to say, okay, if this is a component of that solution, how does it compare to the full solution? In other words, we were trying to disassemble it a bit.

Q. What did you learn was actually in the Purogene?

A. Well, we learned that, through analytical chemistry

techniques, through this methodology, by comparing the different constituents which we understood would be in the stabilized chlorine dioxide, that we came to the conclusion that stabilized chlorine dioxide was chloride, nothing more, nothing less.

Q. **Did it generate chlorine dioxide spontaneously as Bio-Cide claimed?**

A. **We could not find any evidence of spontaneous generation of chlorine dioxide.**

Q. **Was that just at the pH that Purogene was sold at or also in the pH's in the 7 where you said you were working?**

A. **At physiological pH, that was our finding as well.**

Q. **How did you feel when you learned it was just sodium chloride?**

A. **Well, a little disappointed, because, obviously, the mechanisms of action as represented by Bio-Cide, was, I think, as they termed it in their own packet, was amazing. And, indeed, you know, we thought it was amazing and we said, wow, this may be, you know, for us, in contact lens care, would be a breakthrough for us.**

So we felt a bit deflated, and, of course, a bit, you know, depressed about where we were, because we had, you know, spent a good deal of time and energy at this point to get to the place where we kind of had a basic understanding of the toxicities and the antimicrobial

capabilities, and now what really was in it.

Up until this point in time, in dealing with Bio-Cide, they had also always insisted on supplying us the samples. They would not give us any information as to what was in the product so that we could do our own manipulations.

Q. **Did this mean you would have to change your approach for a disinfectant?**

A. **Yes, it did, indeed.**

Q. **What would the changed approach have to be?**

A. **Well, basically, we weren't getting the kill that we needed. So just using the Purogene in this and of itself at concentrations, you saw at a thousand ppm we had irritation. Well, we certainly couldn't take it up to 20,000 ppm or 2 percent then, because we would probably magnify that toxicity.**

So we had to put our thinking caps back on, and what we started looking at was a two-part system. In other words, Purogene at a very low concentration, then we would activate, and we knew how to do that, activate the chlorine dioxide gas at the point in time we wanted to have a disinfectant event. Then the gas would dissipate.

Q. **So you were working to create the gas itself?**

A. **We were working to create the gas itself, because -- and we had experiments that told us that gas, chlorine**

dioxide gas, plus Purogene was very effective.

Q. Did you do studies to determine the feasibility of using the chlorine dioxide itself in a, for example, a bottle of an ophthalmic product?

A. Yes, because the first idea was, okay, let's take the bottle, Purogene, at the appropriate concentration where we could set the toxicity level, where it was acceptable, and then we just simply add in the required amount of chlorine dioxide gas, cap it up, and here is your product.

Q. What were the results of those studies?

A. They were very disappointing.

Q. If I could ask you to turn to the next tab in your notebook, which is Plaintiff's Exhibit 270. Can you identify, generally speaking, this document for the Court?

A. Yes, this is Paul Ripley's laboratory notebook.

Q. If you would turn to Page 55 and 56 of the notebook.

MR. SODIKOFF: Your Honor, we have an objection. Just foundation.

MR. SINGER: I would be happy to.

BY MR. SINGER:

Q. Mr. Dziabo, did you work with Mr. Ripley on a daily basis at Allergan?

A. Yes, I did.

Q. Did you supervise Mr. Ripley?

A. Yes, I did.

Q. **Did you review his laboratory notebook frequently?**

A. **Yes, I did.**

Q. **Have you reviewed his laboratory notebook in the context of your work with Allergan?**

A. **Yes, I have.**

MR. SODIKOFF: We withdraw it.

MR. SINGER: Thank you.

BY MR. SINGER:

Q. **I was referring to Pages 55 and 56. You described a disappointing result. What is this experiment we are looking at?**

A. **This is an experiment where we tested our hypothesis, or we tested, could we keep the chlorine dioxide gas in the container.**

Q. **And I see some numbers on the bottom, on the left-hand side. What are those numbers?**

A. **Those are the results of the experiment. I will give you a brief outline of the experiment.**

Basically, what happened here, what Mr. Ripley did was took ten-milliliter glass vials. He took a solution, and he liberated 25 parts per million of chlorine dioxide gas. And then he filled that into the bottles.

Now, these glass vials, one set he stoppered with a rubber stopper and the other set he left open, with no stopper, put them the hood, and then pulled samples at

various time frames.

So if you want to blow that matrix up there at the bottom of the page.

You can see, in the left-hand column, he has the capped vials. In the right-hand column are the uncapped vials.

At zero time, you can see the column marked C, there is the 23.77 parts per million of the chlorine dioxide gas. As you can see, for the uncapped bottle it is identical. Obviously, this is the beginning of the experiment.

For the capped bottles, you can see that by 360 minutes, we are down to 12.3 ppm. Lost almost half of the chlorine dioxide gas at six hours. Hardly a viable, practical solution for a product that needs to sit on the shelf for two years.

For the uncapped, it's even more dramatic, as you might expect. After six hours, there is hardly any of the chlorine dioxide left.

Q. **Are those results depicted graphically on the next page?**

A. **Yes, they are. That is maybe a better way to conceptualize it here.**

If Mr. Exline can blow that up.

Q. **What is the top line, Mr. Dziabo?**

A. **Okay. Mr. Exline failed to get the far right-hand, which gives you the -- there we go.**

The round circles are capped, the triangles are uncapped. These are the results graphically displayed from the matrix on the previous page.

Q. **Again, could you would you characterize this experiment as a failure?**

A. **In the context of a product that has a practical use of two years, indeed.**

Q. **Mr. Dziabo, what was the next step in the development process of the Purogene product for use in ophthalmics?**

A. **Basically, what we were looking for here, then, is to try to determine some of the further physiochemical effects of the solutions.**

Q. **Now, at some point did you formalize the relationship with Bio-Cide in writing?**

A. **We did, indeed, do that as well.**

Q. **Was there an agreement signed with Bio-Cide?**

A. **Yes, there was.**

Q. **What did this agreement relate to?**

A. **This agreement was an option agreement for a disinfectant product.**

Q. **If I could have you turn to Joint Exhibit 63. Is this that agreement?**

A. **Yes, that is the agreement.**

Q. **And was the agreement focused on disinfectant uses only?**

A. **This agreement was focused strictly on --**

MR. SODIKOFF: Objection, Your Honor. That calls for a legal conclusion.

THE COURT: What was the agreement?

MR. SINGER: It was simply: Was the agreement focused on disinfectant uses?

THE COURT: Overruled. You can answer the question.

THE WITNESS: Yes.

THE COURT: I don't think that calls for a legal conclusion.

MR. SINGER: I will ask one followup to make it clear, Your Honor.

BY MR. SINGER:

Q. **Is attached to the agreement, Mr. Dziabo, the standards for disinfecting solutions, at Attachment 1?**

A. **Yes, there is.**

Q. **That is at Allergan 0730498?**

A. **That's correct.**

Q. **Are there standards for preservatives attached to this agreement?**

A. **No, there are not.**

Q. **Thank you. Okay.**

What was the benefit of signing the agreement with Bio-Cide? You said that the product was just sodium chloride. Was there advantages to working with Bio-Cide nonetheless?

A. **Yes. We discussed that at some length, obviously, before signing this agreement, because we had that knowledge prior to negotiations. And the advantage was that the only supplies of chloride available in the marketplace were fairly impure. They were only like 80-percent purity. That means there was 20 percent of who knows what. And it would have taken us a great deal of time and money to characterize what those impurities were, and also to determine how they varied over time. And that really was adding no value to the project.**

So the process that Bio-Cide used to produce the Purogene produced a relatively pure, consistent source of sodium chloride.

So we felt it was to our advantage to continue our relationship with Bio-Cide in this regard.

Q. **Now, after entering the agreement, did you do additional work trying to add chlorine dioxide to the Purogene to prove its efficacy?**

A. **Yes, we did.**

Q. **I would ask you to turn to the next tab in your binder, Plaintiff's Exhibit 573, if we could put that up on**

the screen. What is this experiment described, Mr. Dziabo?

A. **This experiment basically was done to look at antimicrobial activity of solutions with different concentrations of free chlorine dioxide gas in the Purogene.**

Q. **And what happened when you added free chlorine dioxide to Purogene?**

A. **It basically took off, from an antimicrobial perspective, the troublesome organism, the Aspergillus niger. We were now able to eliminate it.**

Q. **If I could have you turn to Table 1, where it has the results. You said it took off. Where do we see that in this table?**

A. **If I might suggest we take a look at the following page, it might be a little easier, because we have already talked about how these tables work. Take a look at the A. niger, you can highlight the A. niger at the bottom, Mr. Exine, please.**

Okay. You may need to blow that up a little.

Q. **I think we are at the limits --**

A. **Is that it?**

Q. **Okay.**

A. **Very simple here. As you can see, for the solutions starting with the first column, it is regular Purogene, what we see there and what we had always seen with A. niger, that was noculum. The additional noculum 8 times 10-to-the-5,**

you can see we are 8 times 10-to-the-5 the whole way down. With the addition of the chlorine dioxide, we see total destruction of the A. Niger.

Q. **The A. Niger was the thing you had trouble killing before?**

A. **You see the Purogene up there. You see the results.**

Q. **Thank you, Mr. Dziabo.**

A. **The answer to your question is yes.**

Q. **Mr. Dziabo, did you also study more scientifically the claim Bio-Cide had made about the spontaneous generation of chlorine dioxide?**

A. **Yes, we did, the so-called reservoir effect, because that was one of the things that attracted us to this conceptualization of the stabilized chlorine dioxide in the first place.**

Q. **Just briefly, what was the reservoir effect again? I know we have said it. Just for the record?**

A. **Chlorine dioxide gas would be generated on demand under certain conditions.**

Q. **And what were your findings as to whether or not there was a reservoir effect?**

A. **Our experimentation showed us there was no reservoir -- the reservoir effect was negligible.**

Q. **If you could go back to what we have marked as Plaintiff's Exhibit 270, Mr. Ripley's notebook. I will**

refer you to Page 105, which is at Allergan 0911919.
A. What was the page number?
Q. '0911919, it is probably easier to look at the page in Mr. Ripley's notebook.
A. I have that.
Q. What experiment is Mr. Ripley conducting here?
A. This is the experiment to determine if, indeed, there was a reservoir effect as described by Bio-Cide.
Q. What was the conclusion with respect to whether or not there was a reservoir effect?
A. If we could look at the next page, I believe it has Mr. Ripley's conclusion.
Q. If we could highlight the bottom of the page?
A. The bottom paragraph.
Q. What does that say?
A. Basically, what it says here is that, once the solution dropped to 0 ppm ClO2 -- I better start from the top. I am having problems reading that. I am sorry.
Q. We will highlight there at the bottom?
A. Can we go back down to the bottom there?
Q. Thank you. The bottom paragraph. Thank you. I will help you.
A. It's 47.4 parts per million of potential ClO2 was consumed when the solution was acidified. However, since the bulk of the potential ClO2 was remaining after the

solution dropped to a zero ppm of chlorine dioxide gas, ClO2 gas, there cannot be a reservoir effect. There could only be a substantial reservoir effect if there was no potential CO2 left in the final solution.

Q. **Now you have debunked most of what -- most of what Bio-Cide has told you about this product and learned for yourselves what it really is. Were you and Mr. Ripley brainstorming other ideas to use the Purogene?**

A. **Well, yes, we were. As you mentioned before, you know, we communicated on a daily basis, if not, even more often than that, especially from an experimental standpoint. And we had gathered a substantial amount of data, characterizing the Purogene solution, from a pH osmolarity. Antimicrobial effects versus concentration. Antimicrobial effects versus PE. Antimicrobial effects versus toxicity. Et cetera, et cetera.**

So we started to look through this to see if we could pull out something of value or if we could recognize something of value in this regard.

This is when we started to really conceptualize the issue, the possibility of the Purite as a preservative.

Q. **Did you run tests to see if your preservative idea would work?**

A. **We were running tests on many different products at this point in time, yes.**

Q. **And where was this work done?**

A. **Some of the earliest work was done with regards to our RGP products.**

Q. **What is an RGP product?**

A. **There are two basic classes of contact lenses. There are soft lenses, which most people are familiar with. They dominate in the marketplace. They are a hydrogel, and they are soft. And there are rigid gas-permissible lenses, RGP. They are rigid and hard, and they address some specific visual correction problems that the soft contact lens cannot.**

So there is two basic categories. Nevertheless, the RGP lenses need to have their care products as well.

Q. **What was your role in the RGP group?**

A. **The RGP Products group also reported to me.**

Q. **I want to refer you to the next three documents in your binder together, Plaintiff's Exhibit 596, 581 and 580. If we can put all three up. It will be hard to read but we will make it legible.**

First off, let's look at the dates. When was the experiment in Plaintiff's Exhibit 596 done?

A. **That date of the experiment is dated September 4th, 1986.**

Q. **Looking at Plaintiff's Exhibit 581, when was that experiment done?**

A. **That experiment was done the next day, on September 5th, 1986.**

Q. **Then looking at Plaintiff's Exhibit 580, when was that experiment done?**

A. **On 9/9/86.**

Q. **What are these battery of tests that you are running on the Purogene in the RGP group, generally?**

A. **Generally, what is done here is what's called the design of experiments. A series of experiments are put together, usually the formulation group requests these, looking at testing various parameters in the solution which are important for us to gather experimental information on.**

In this case, it was the microbiology of the product which we called Wet-N-Soak, which was the RGP Care product. And we were looking at possibly the use of the Purogene as an antimicrobial agent for the Wet-N-Soak products.

Q. **Were preservative efficacy tests run, Mr. Dziabo?**

A. **They were.**

Q. **Where do we see that in this battery of tests?**

A. **You can see it best on -- let's see which one of these? I have all three of them.**

Q. **If it would help, I draw your attention to Plaintiff's Exhibit 581?**

A. **581 is the best one, yes.**

Q. **What does it say there?**

A. **In this case, it says that 200 parts per million of Purogene with the Wet-N-Soak formula, it had a problem with antifungal activity and also the yeast. But it basically passed U.S. PET.**

Q. **Are U.S. PET the preservative efficacy standards?**

A. **That's correct.**

Q. **What was your reaction to these results?**

A. **Very encouraging, and very exciting, because we initially had looked at this product as a disinfecting agent. We thought we had hit a bit of a wall in that regard, but now it appeared there was an alternative use, an exciting new preservative use in the realm of preservation.**

Q. **Did you tell Bio-Cide about it?**

A. **Yes, we did.**

Q. **Were they excited about it?**

A. **They were quite excited about it, as you can well imagine.**

Q. **What happened as a result of these results you got from the RGP group?**

A. **Another meeting.**

Q. **If I could refer -- who was that meeting between?**

A. **This was between representatives from Allergan and Bio-Cide.**

Q. **Was it just you and Mr. Danner this time, or were**

there a whole bunch of people this time?
A. No. There were senior representatives from both companies.
Q. If I can refer your attention to Defendant's Exhibit 226. This is a memo you authored. Is that correct?
A. That's correct.
Q. What is this memo?
A. This is minutes of a meeting, action items, actually, that resulted from the Allergan-Bio-Cide meeting.
Q. I refer your attention to the second page of the memorandum, Bio-Cide 534. And Paragraph 2. What does it say in Paragraph 2 was going on?
A. This basically discussed the development approach with the Purogene products, the stabilized chlorine dioxide products. And as always, you know, Bio-Cide was very interested in how soon are we going to get to the market so we can generate an income stream. We, of course, wanted to be sure that we had substantiation of safety and efficacy because we are responsible.
So we came up with a strategy for moving forward. And that strategy said that the first product that we were going to basically look at would be preservation of normal saline. The second product would be a binary disinfection system, two-part system. And the reason for that is, as we had been unsuccessful in a one-bottle type

system up to that point in time, but we still felt confident that we could release that chlorine dioxide gas on demand, and that would satisfy our disinfection.

However, the ultimate goal would have been a one-bottle system, because a two-part system, you have to understand, you know, when you can do one instead of two, guess what the patient will choose?

All right. So the ultimate embodiment of this technology would be the item C, which is a one-step system or one-bottle system.

And this was the strategy, so to speak, that was laid out in this meeting.

Q. **Looking at Paragraph 3, what does that talk about in the memo?**

A. **In this instance, Hampar Karageozian, who was the senior vice president for R&D at Allergan at this point, he proposed that the existing contract be amended to include preservation in light of these proposed strategies.**

Q. **And it was also amended in light of the results you had gotten --**

A. **And the results, absolutely, the results.**

Q. **And then, moving forward, in Paragraph 4, what does Paragraph 4 say?**

A. **That basically stated the fact of Allergan's intent to move forward with the preservation concept with the normal**

saline.

Q. **Was the Bio-Cide-Allergan agreement amended in fact?**

A. **It was indeed.**

Q. **If you could turn to the next document in your binder, which is Plaintiff's Exhibit 375. Do you have that in front of you?**

A. **Yes, I do.**

Q. **Can you identify this document for me, please?**

A. **Yes. This is the letter, the cover letter to Hampar Karageozian from Bill Knapp at Bio-Cide, indicating that they have signed the option agreement, the use of, he says our chlorine dioxide. What he means is the stabilized chlorine dioxide, the Purogene, as a preservative for ophthalmic products.**

And the next page, you will see here, is the actual copy of the signed document.

Q. **This is the first reference in the Bio-Cide-Allergan written agreement relationship to preservatives. Is that correct?**

A. **That's correct.**

Q. **You have signed the agreement now, after you have done the work on the RGP. Did you bring the product forward in the buffered saline?**

A. **Yes, we started down the pathway towards completing the project development and commercial release.**

Q. **If you could turn to the next document in your binder, Plaintiff's Exhibit 583, can you identify this document for me, please?**

A. **Yes. This is a microbiology test again. The Allergan research microbiology group, AMEM, microbe effectiveness, PET, observed the effective testing of Purogene in isotonic borate buffer.**

Q. **Is this a test with respect to the preserved saline project?**

A. **Yes, it is.**

Q. **In the meantime what were happening with those preservative solutions from Wet-N-Soak?**

A. **Unfortunately, we had another back-to-the-drawing-board moment. We, the next step in the process after defining antimicrobial activity and toxicity is now do we have a stable product, because, practically, speaking, you need two-year shelf life. What we did is entered on what we called accelerated stability testing. The principle there is that, if you store product at a high temperature, it basically speeds up time so that you can get a read on the ultimate shelf life of the product by assaying at various points in time at the higher temperature.**

I am sorry if I wasn't clear there.

The point being the higher temperature mimics a longer time at room temperature. And the results of those

tests were that we were basically falling out of stability, the Purogene was dissipating within two to three months.

Q. **Did that surprise you?**

A. **It did. It did, because, well, it surprised us and alarmed us, because the question there is what's it going to do in the other product categories from a stability standpoint.**

Q. **Did you then have to run stability studies on the buffered saline products?**

A. **We did.**

Q. **I would ask you to turn to -- first off, did you work with the concentration in the buffered saline product?**

A. **Yes, we did.**

Q. **I would ask you to turn actually to the next document in your binder, which is 584, just to briefly talk about the work with concentration. What is this document we are looking at?**

A. **Again, this is a report of the results of test PET on borate buffered saline with 50 ppm of Purogene.**

Q. **Does it pass the U.S. PET?**

A. **It does past the U.S. PET.**

Q. **Now get back to the stability, the stability failure. Did you run the stability study on the buffered saline?**

A. **We immediately acted to complete an accelerated stability study on the saline.**

Q. **If you could turn in your binder to the next exhibit, Plaintiffs' Exhibit 589, what is that document?**

A. **This is a report from the R&D group, from Tony Frangione, Tony reported to Paul Ripley, he was a tech working for Paul Ripley. This is an elevated temperature stability study of borate buffer saline. We put it at elevated temperature. The generally accepted principle is if you can get through 90 days at 45 degrees C, that is equivalent to two years at room temperature. That's why it's accelerated study.**

If you look at the matrix at the very bottom of this page, basically, the samples were put up, and there was three samples, as you can see, on days he wrote the average of the Purogene concentration was 54.4. And the pH, of course, pH is important as well, we have to have stability and pH, by eyeball there, it's about 7.33. At 30 days, we had 53.24, and the pH has not moved hardly at all. At 60 days, we have 52.56, again, the Ch is very solid. Even at 90 days accelerated testing, we had 52 ppm of the Purogene and pH, again, very, very sold.

So this was very heartening thing, very surprising, and very exciting, because this was the first time we saw that we had everything that we needed for a product.

We had the -- antimicrobial activity with

regards to PET, we had the toxicity down to 50 ppm, we had the stability. We had the stability with a pH at physiological. These solutions all were isotonic.

This gave us a great deal of confidence that we were on the right track to commercializing this product.

MR. SINGER: Your Honor, as it happens, I am at a very convenient breaking point. I have 15 minutes left. Would you like to break for the day?

THE COURT: Let's finish your direct.

MR. SINGER: Okay.

BY MR. SINGER:

Q. Now, about this time, Mr. Dziabo, despite these good results, was Bio-Cide expressing impatience with the pace of progress on the Purogene?

A. Well, I would constantly get calls from Mr. Knapp and Mr. Danner from Bio-Cide saying what's taking you so dang long? Let's move it. Let's go. What can we do ? What can we do to help?

Q. Did Mr. Danner express that impatience to you personally?

A. Yes, he did.

Q. What did you do in response?

A. Basically, what I did was I put together what I would call a shopping list of items and data that we would need as part of our commercial release package.

Q. **And if I refer to the next exhibit in your binder at DTX-346?**

A. **Yes.**

Q. **Do you have that in front of you?**

A. **I do.**

Q. **Is this the letter you wrote with that shopping list?**

A. **It is, indeed, to Mr. Knapp at that time.**

Q. **This was all after you had done the work on characterizing the Purogene as a preservative?**

A. **Yes, it was.**

Q. **Did you receive a response from Bio-Cide on all of these questions?**

A. **We did receive some information, but very, very little. In the end, basically, Allergan had to cover all of these bases with our own either internally generated or reference material.**

Q. **Did you and Mr. Ripley file for a patent for your discovery that the sodium chloride or stabilized chlorine dioxide could be used in and of itself as a preservative?**

A. **Yes, we did.**

Q. **I would ask you to look at Joint Exhibit 1. It should be the next document in your binder.**

A. **Yes.**

Q. **Is this that patent?**

A. **Yes, it is.**

Q. **And are you listed there with Mr. Ripley as the inventors?**

A. **Yes, we are.**

Q. **What stands out for you in the process of obtaining the patent?**

A. **Probably the most remarkable thing was how long that it took.**

Q. **Was it an arduous process, as you understood it?**

A. **Yes, it was an arduous process. It was, you know, bringing everybody up to speed on the technology. Getting the technology reduced into, you know, into pieces that can be, you know, represented in the patent. Understanding all the reference materials. And getting it written and getting it prosecuted.**

Q. **Do you understand that there was an appeal that related to your patent at the United States Patent and Trademark Office?**

A. **Yes, I do.**

Q. **Did you win that appeal?**

A. **My understanding was the appeal was -- we did win the appeal and the patent was issued.**

Q. **I would like to look at Claim 1 of the patent, if we could. If we could just put the two halves together on the screen, I think it will make this go a little faster.**

The first clause in the claim is, a method for

preserving an aqueous ophthalmic formulation, et cetera. Do you see that?

A. **Yes.**

Q. **The term ophthalmic, what does that refer to?**

A. **Any type of product that's used in or around the eye.**

Q. **How does that differ from what you were doing at State Chemical, for example?**

A. **Well, again, tabletops don't scream. State Chemical, they were inanimate objects, hard surface disinfection.**

Q. **You will see in the second line it refers to enhancing the shelf life. Again, what was generally understood in the field to be the minimum shelf life?**

A. **The minimum practical shelf life for a product is, has been determined to be two years.**

Q. **Then the next phrase says, if we could highlight, "comprising incorporating into said aqueous ophthalmic formulation stabilized chlorine dioxide in an amount effective to act as the sole preservative."**

Do you see that?

A. **Yes.**

Q. **Have you seen a definition in the patent for stabilized chlorine dioxide?**

MR. SODIKOFF: Objection, Your Honor. This seems to be getting into claim construction.

MR. SINGER: I don't need to ask that question.

BY MR. SINGER:

Q. **What is the stabilized chlorine dioxide, as you understand it?**

A. **It is the chloride solution.**

Q. **Then it says it acts as the sole preservative. What does that mean?**

MR. SODIKOFF: Objection, Your Honor. This is again claim language. I don't know if he is qualified to interpret it.

MR. SINGER: I am just asking for what his understanding of his claimed invention is.

THE COURT: Overruled.

THE WITNESS: -- is that the predominant, primary agent that's affecting preservation is the stabilized chloride dioxide by sinks.

Q. **Is it the gas or is it the chloride?**

A. **It's the chloride.**

Q. **And then, the next part of the claim is a pH, it says that there is a buffer component in an amount effective to maintain said aqueous ophthalmic formulation at the pH in the range of about 6.8 to about 8.**

Do you see that?

A. **Yes.**

Q. **Why is that important?**

A. **Again, the optimal situation for patient safety and**

comfort is to match the native pH of the eye.

Q. In that claim pH range, it is your understanding, that it is chlorida doing the antimicrobial action?

A. That's correct.

Q. Is that different from what Bio-Cide told you when they walked in the door all those years ago?

A. That's correct.

Q. And is that a different pH than what Bio-Cide provided you?

A. It was, Bio-Cide's Purogene was formulated at 8.5 to 9.0.

Q. When did they say when you dropped the pH in the 7s would happen?

A. They said you would dilute it. You would drop it. The addition would cause the liberation of carbon dioxide.

Q. The last couple of phrases refer to the osmolarity, at least one acceptable tonicity component. We talked a little bit about osmolarity. Then I want to focus on the last phrase, which talks about no germicidally effective amounts of any positively charged, nitrogen containing cationic polymers. What does that refer to in your understanding?

MR. SODIKOFF: Objection, Your Honor. We have had a claim construction.

THE COURT: I am capable of recollecting how I construed the terms.

MR. SODIKOFF: Thank you, Your Honor.

BY MR. SINGER:

Q. **What is your understanding of that?**

A. **I can answer it?**

Q. **Yes, I think you can.**

A. **Again that basically means that there is no quaternary ammonium compound in the solution.**

Q. **And quaternary ammonium compound is another type of preservative?**

A. **It's a commonly used preservative in the classification of the quaternium that we previously used in the AHDS, and also like benzylalkonium chloride as well.**

Q. **Do you believe you and Mr. Ripley are the inventor of this claim?**

A. **Absolutely.**

Q. **Do you believe you are the inventor of the other claims in the patent?**

A. **Absolutely.**

Q. **Have you heard accusations in this case that you are not the inventor of these claims?**

A. **Yes, I did.**

Q. **And that they were invented by Bio-Cide?**

A. **Yes, I have.**

Q. **What do you think of those?**

A. **I would say that that is incorrect. The**

conceptualization and the inspiration to take this product into the preservative range, that is the stabilized chlorine dioxide, was solely the invention of Mr. Ripley and myself.

Q. **Have you also heard accusations in this case that you weren't candid with the Patent Office?**

A. **Yes, I have.**

Q. **Do you understand that one of those accusations is that you didn't show the Patent Office a patent application that Bio-Cide had filed?**

A. **That's correct.**

Q. **Before being shown it in your deposition in this case, do you recall ever seeing that patent application before?**

A. **I have no recollection of that event.**

Q. **You have also been accused of withholding information from the Patent Office related to toxicity. Do you understand that?**

A. **Yes, I do.**

Q. **Are you aware that one of those accusations relates to the so-called Wentworth '521 patent?**

A. **Yes, I am.**

Q. **I will refer you in the binder to the last document in your binder, Defendant's Exhibit 130, which is the Wentworth patent. Do you have that in front of you, sir?**

A. **Yes, I do.**

Q. **First off, Mr. Dziabo, is that piece of prior art**

cited in your patent?

A. **Indeed, it is. It is actually the fourth citation under the references cited U.S. patent documents.**

Q. **I am going to refer you to some specific information in the Wentworth patent and Column 3, on the second page of Defendant's Exhibit 130, where it says E, do you see that there?**

A. **Yes.**

Q. **"Installation of a one to 240 dilution of dioxide was non-irritating in guinea pigs." Do you see that?**

A. **Yes, I do.**

Q. **What does that say to you about the suitability of stabilized chlorine dioxide in your experience in ophthalmic formulations?**

MR. SODIKOFF: Objection, Your Honor. Calls for a legal conclusion -- I am sorry, an opinion.

THE COURT: Mr. Singer.

MR. SINGER: Mr. Dziabo is being accused of inequitable conduct for not disclosing this information. He has talked about toxicity information, what is and not relevant to his experience.

THE COURT: I understand. The objection is overruled.

MR. SODIKOFF: Your Honor, we just don't -- I don't think we have made an accusation anywhere against Mr.

Dziabo.

MR. SINGER: If --

THE COURT: If the issue --

MR. SINGER: If the issue is withdrawn, I can conclude my examination.

MR. SODIKOFF: We do have an inequitable conduct defense. But we have not made specific accusations that --

THE COURT: That is counsel's interpretation of the defense that has been advanced. You will have an opportunity to examine on this.

MR. SINGER: Thank you, Your Honor

BY MR. SINGER:

Q. **I was asking you, Mr. Dziabo, as someone who worked in the area of ophthalmic formulations, what does this guinea pig data in the Wentworth patent say to you?**

A. **It really does not give me any substantive information in that the guinea pig model has never been the one relied on for in vitro, in vivo testing of ophthalmic products.**

Q. **That was a rabbit model we saw before?**

A. **The models you saw previously were all rabbit models.**

Q. **Lastly, do you understand that you have been accused of withholding the Still Meadow toxicity studies from the PTO during examination at the United States Patent Office?**

A. **Yes, I have.**

Q. **And we can go back to those, those are Defendant's**

Exhibit 348. They are near the front, Mr. Dziabo, about the sixth or seventh document in?

A. **Yes, I have got it.**

Q. **Just to conclude, what were the results of this Still Meadow toxicity study for the Oxine product?**

A. **Again, if you turn to the page Bio-Cide 0000742, under the summary document, the last paragraph, "The test material was minimally irritating in non-washed eyes and mildly irritating in washed eyes."**

Q. **Was that a negative concern to you about the suitability of stabilized chlorine dioxide as an ophthalmic preservative?**

A. **Indeed, it was a concern.**

MR. SINGER: I have no further questions, Your Honor.

THE COURT: We will have cross-examination tomorrow. We will adjourn for the evening.

(Court recessed at 5:10 p.m.)

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